SYNTHESIS OF THIAZOLIDINONE DERIVATIVES CONTAINING THIADIAZOLINE MOIETY OF BIOLOGICAL INTEREST

A DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENT FOR THE DEGREE OF MASTER OF PHILOSOPHY (M. Phil) IN CHEMISTRY

SUBMITTED

BY

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THESIS ACCEPTANCE LETTER

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Author

(Md. Shahin Azad)

Dedicated

To

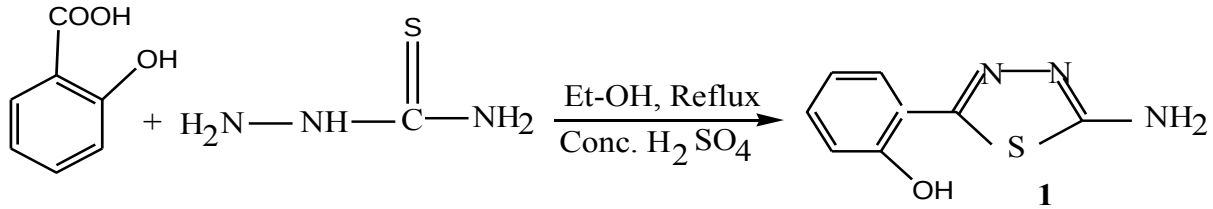
My Family

Contents

ABSTRACT

The synthetic precursor thiadiazole (**1**) has been synthesized from salicylic acid and thiosemicarbazide under reflux condition. Condensation of thiadiazole with different substituted benzaldehydes produces hydrazone (**2-7**). The reaction of different hydrazones with mercapto acetic acid in presence of catalytic amount of zinc chloride affords the substituted thiazolidinone derivatives containing thiadiazoline moiety (**8-13**). All the synthesized compounds were characterized by IR, ^{1}H NMR and ^{13}C NMR spectral evidences. The newly synthesized thiazolidinone compounds were tested for the antibacterial and anti fungal activity against *Escherichia coli* (*E.coli*) and *Aspergillus niger* (*A.niger*) respectively. The testing results showed moderate activity against *E.coli* and *A.niger*.

1. Synthesis of amine

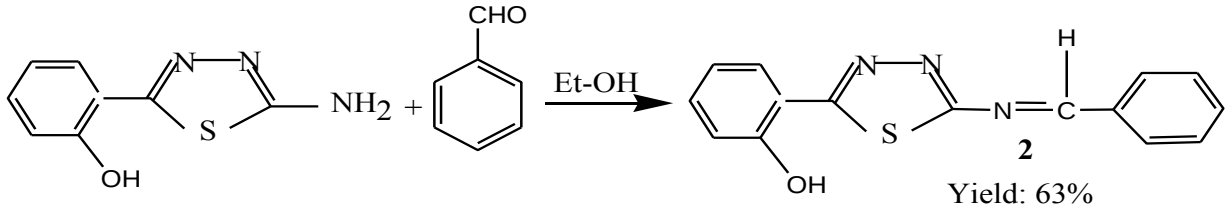


1

Yield : 82%
m.p :(145-150) ^{o}C

2. **Synthesis of hydrazones**

(a)



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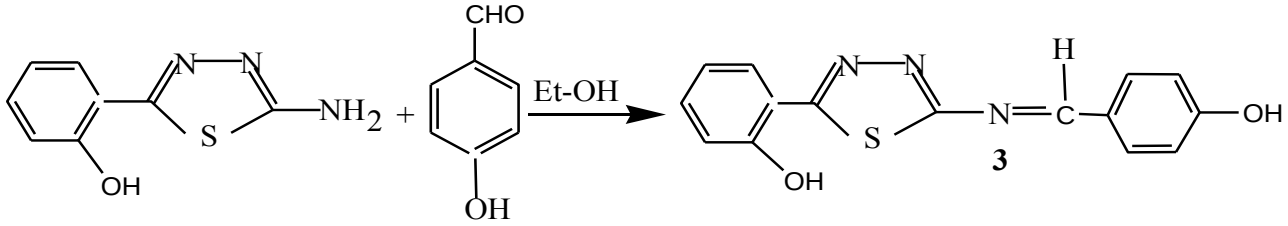
Yield: 63%

m.p:(162-165) ^{o}C

(b)

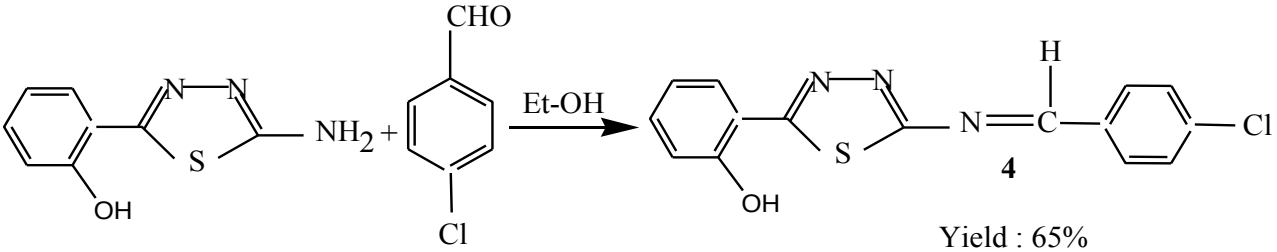


3

Yield :71%

m.p:(218-221) ^{o}C

(c)



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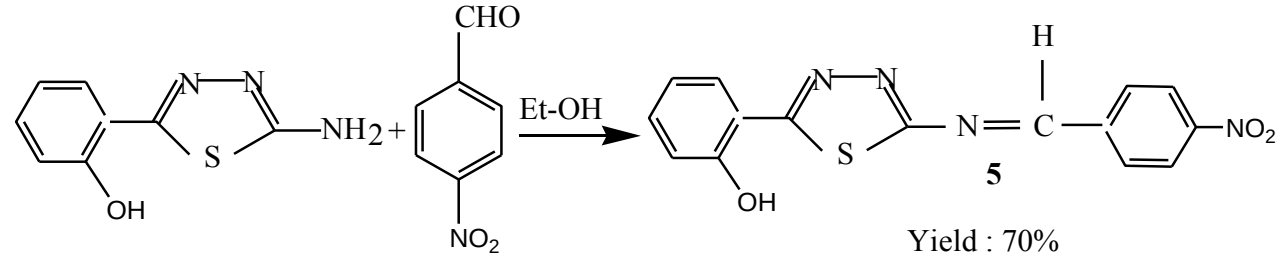
Yield : 65%

m.p:(219-220) ^{o}C

(d)



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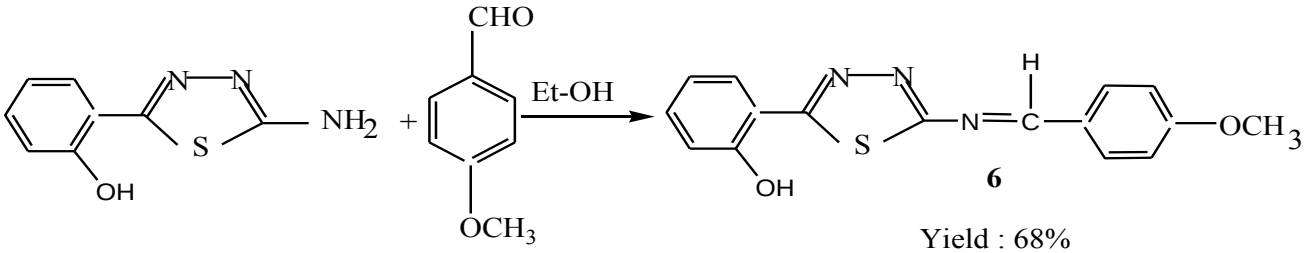
Yield : 70%

m.p :(237-239) ^{o}C

(e)

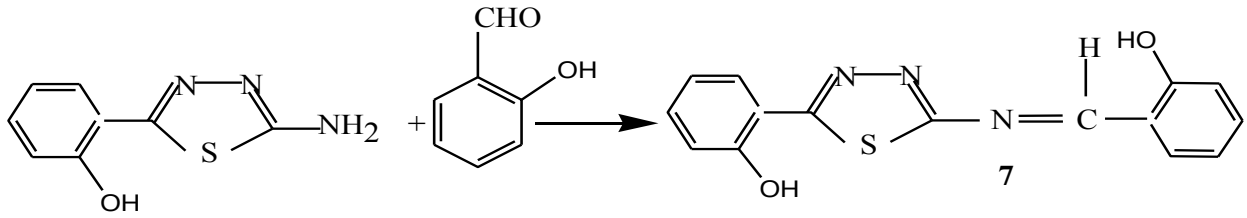


6

Yield : 68%

m.p :(172-178) ^{o}C

(f)

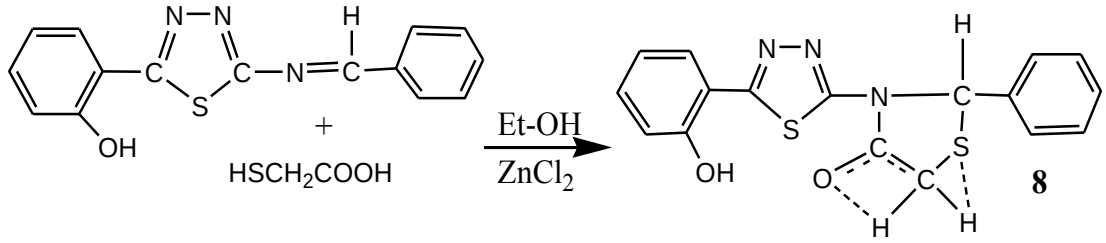


7

Yield : 73%
m.p :(195-203) ^{o}C

3. Synthesis of Thiazolidinone dervatives

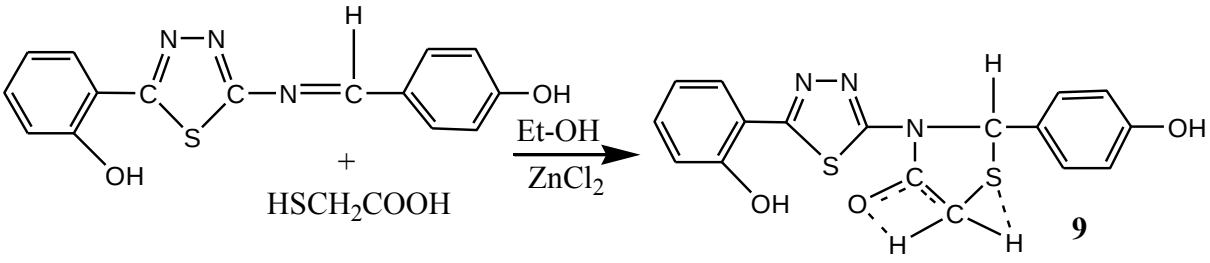
(a)



8

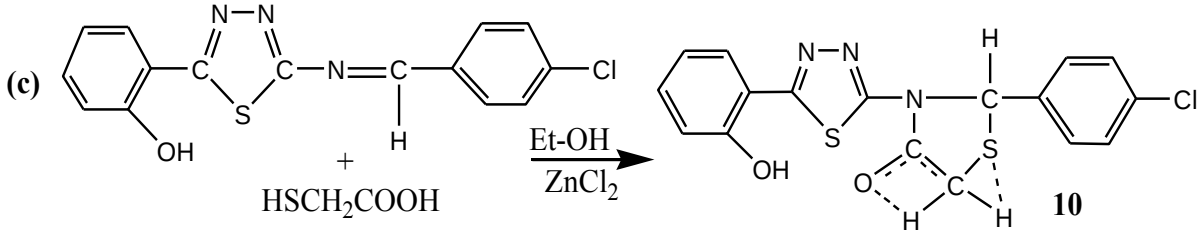
Yield : 67%
m.p: (178-185) ^{o}C

(b)

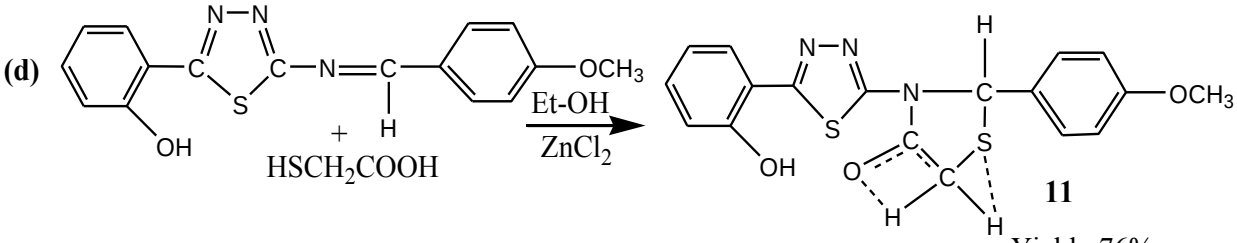


9

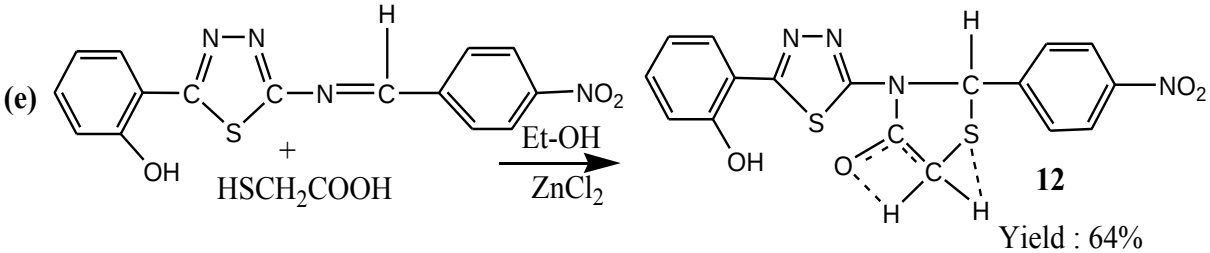
Yield : 62%
m.p :(239-241) ^{o}C



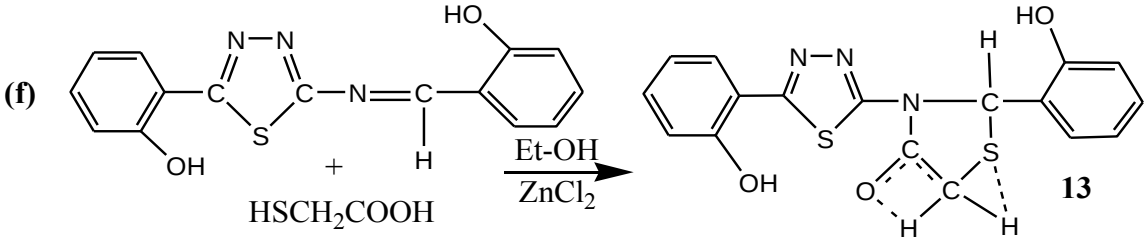
Yield : 78%
m.p:(206-209) ^{o}C



Yield : 76%
m.p:(279-281) ^{o}C



Yield : 64%
m.p:(243-245) ^{o}C



Yield : 69%
m.p:(216-219) ^{o}C

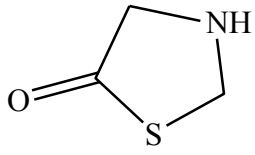
4. Biological activity

The antibacterial and antifungal properties of thiazolidinone derivatives **10** and **11** showed moderate activity against *Escherichia coli* and *Aspergillus niger*.

Chapter 1
Introduction

1. Introduction

Heterocyclic compounds containing nitrogen and sulphur play an important role in the design and discovery of new physiologically and pharmacologically active compounds. Medicinal chemistry deals with the design, synthesis and production of molecules having therapeutic value. During the past few decades growth in areas like combinatorial chemistry and heterocyclic chemistry has lead to development of many privileged structure with proven utility in medicinal chemistry [1]. Thiazolidinone, a saturated form of thiazole with carbonyl group on fourth carbon, has been considered as a magic moiety (wonder nucleus) which posses almost all types of biological activities. It belongs to an important group of heterocyclic compounds containing sulfur and nitrogen in a five membered ring [2]. This biologically active scaffold has encouraged interest in synthesizing several new compounds by using several substitutions at different positions, attached to 4-thiazolidinone moieties. Substitution can have at 2, 3 and 5 positions. Substituent at 2-, 3- and 5- positions may be varied, but the greatest difference in structure and properties is exerted by the group attached to the carbon atom in the 2-position [3]. Tetrahydro derivative of thaiazole is known as thiazolidine and the oxo derivative of thiazolidine is known as thiazolidinone.



1

Thiazolidinone

The 3-unsubstituted thiazolidinone are usually solids, often melt with decomposition, but the attachment of an alkyl group to the nitrogen lowers the melting point. The thiazolidinone that do not contain aryl or higher alkyl substituents are somewhat soluble in water [4]. Thiazolidinones are known to exhibit anti-tubercular [5], antibacterial [6], anticonvulsant [7], antifungal [8] and anti-thyroid activities [9]. Some of thiazolidinone derivatives were found to show interesting anti-HIV and anticancer activities [10]. Thiazolidinone, with carbonyl group at 2, 4 or 5 positions have been subjected to extensive study in the recent years. Numerous reports have appeared in the literature, which highlights their chemistry and use [11]. It was observed that

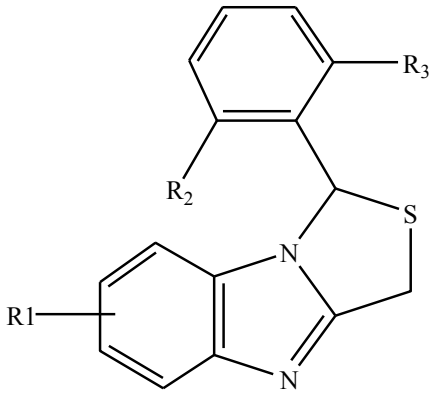
reaction with cyclizing reagents like α-halocarbonyl compounds such as $ClCH_2COCl$, $BrCH_2COCl$, $BrCH_2COOEt$ and $ClCH_2COCH_2COOEt$ in boiling ethanol with fused sodium acetate have better biological profiles as thiazolidinone [12]. Thiazolidinone and its derivatives have been reported to possess a variety of pharmacological properties. 4-Thioozolidinones are known to exhibit anti-tubercular [13], antibacterial [14-15] and antifungal [16] activities and also reported as HIV-1 RT inhibitors [17-18]. Apart from the substructure of widely used antibiotics [19] such as penicillin, cephalosporin, monolactams, etc. the acetidin-2-one (α-lactam) skeleton has been synthetic intermediates and biologically active precursor [20]. A large number of 3-chloro monocyclic α-lactams possess powerful antibacterial, antimicrobial [21], anti-inflammatory [22], anticonvulsant and anti-tubercular activity. They also function as enzyme inhibitors and are effective on the central nervous system. 4-Thiazolidinone and 2-azetidinone derivatives occupy an important place in medicinal chemistry as they show a variety of microbiological activity. The compounds were screened for their antibacterial activity against *E. coli, P. aeruginosa, S. aureus and bacillus sp*. The minimum inhibitory concentration (MIC) was determined using Disk Diffusion method according to the standard procedure at three test concentration, 128 μg/ml, 256 μg/ml and 512 μg/ml. DMF was used as a blank. Standard antibacterial Streptomycin was also screened under the similar conditions for the comparison. The importance of the quinoline nucleus has been well demonstrated as illustrated by the large number of patents employing such species as chemotherapeutic agents. A number of biological activities have been associated with quinoline-containing compounds such as anti-inflammatory, antiallergic [23], antimalarial [24], antibacterial [25], antiproliferative [26], anticancer [27-28] and antiparasitic [29] activities. Similarly, various thiazolidinones [30-31] have attracted considerable attention as they are also endowed with a wide range of pharmaceutical activities including CNS-depressant [32], anaesthetic [33], anticonvulsant [34], antibacterial [35-36], antiviral [37] and antitumor [38]. Furthermore, drug research and development has led to the discovery of new pharmacologically active agents, including imidoxy [39-40] compounds such as phthalimidoxy [41] and succinimidoxy [42]. Succinimidoxy derivatives were tested against different cancer cells [43] and also have been used in peptide synthesis [44]. They also possess a strong anticonvulsant activity [45]. Tuberculosis (TB), an infection of *Mycobacterium tuberculosis* still remains the leading cause of worldwide death among infectious diseases. One-third of the population is infected with *M. Tuberculosis* and the World Health Organization

(WHO) estimates that within the next 20 years about 30 million people will be infected with the *bacillusp* [46]. Active disease

following new infection, as well as reactivation of latent tuberculosis, is particularly prevalent in individuals with compromised immune systems, such as those that are HIV positive. Duration of the treatment of cases is very prolonged especially when caused by resistant bacteria. Although advances in cancer detection and treatment over the past 10 years have led an increase in the expected survival period, the majority of patients diagnosed with the disease relapse after cytoreductive surgery and standard adjuvant chemotherapy. While much research is being done to establish active salvage regimens, successful treatment depends upon effective adjuvant therapy. Intrinsic or acquired resistance of cancer cells to chemotherapeutics in several malignant tumors decrease the response rate and new therapeutic agents are needed. Indole derivatives have been shown to possess antibacterial, antifungal and anti HIV activities [47-52]. There have also been several reports on the anticancer properties of compounds bearing this ring system [53-54]. A very recent report deals with the apoptosis inducing effect of 5-methyl-3-phenyl-indole-2-carboxylic acid benzylidene hydrazides. On the other hand, 4-thiazolidinones and their spiroheterocyclic analogs have been reported to exhibit antibacterial, antifungal and anti-mycobacterial activity [55-62]. Furthermore 2-aryl-4-oxothiazolidin-3-yl amides have been reported to demonstrate anti-proliferative activity in prostate cancer [63]. As a consequence of this research and with the aim of obtaining new and more potent anti-tuberculosis and antitumor compounds which can improve the current chemotherapeutic anti-tuberculosis and antitumor treatments. Reverse transcriptase (RT) is a key enzyme which plays an essential and multifunctional role in the replication of the human immunodeficiency virus (HIV) [64] and thus represents an attractive target for the development of new drugs useful in AIDS therapy [65]. RT is necessary for the catalytic transformation of single stranded viral RNA into the double-stranded linear DNA which is integrated into host cell chromosomes. Non-nucleoside RT inhibitors (NNRTIs) bind in a noncompetitive manner to a unique site on the enzyme, altering its ability to function and achieving a highly selective suppression of HIV-1 replication with little cytotoxicity [66]. X-ray crystallographic studies of NNRTI/ RT complexes have shown that the NNRTIs, unlike their structural diversity, present a very similar conformational “butterfly-like” shape [67]. Presently, three NNRTIs, namely nevirapine, delavirdine, and efavirenz are available in clinical practice. Combination of these drugs with nucleoside RT inhibitors and protease

inhibitors leads to a dramatic decrease of the viral load in most of the HIV-infected patients. However, in view of the increasing incidence of resistance to current drug regimens and the frequency of adverse events, the development of novel, selective, potent, safe, inexpensive antiviral agents, that are also effective against mutant HIV strains, remains a high priority for medical research. In previous papers [68] we reported a series of 1-aryl- 1*H*,3*H*-thiazolo [3,4-*a*] benzimidazoles (TBZs) (Compound- 2), which proved to be highly active as HIV-1 NNRTIs. Extensive structure-activity relationship (SAR) studies were performed, and specific requirements were observed with regard to the structural determinants for optimum anti-HIV activity. The C-1 substituent plays a decisive and crucial role in the interaction of TBZ compounds with the target HIV-1 RT: in particular a 2, 6-dihalo-substituted phenyl ring at C-1 gave a large improvement in potency. The author have also demonstrated, by Comparative Molecular Field Analysis (CoMFA) and flexible docking experiments [69], that the biological activity of TBZs is associated with their ability to assume a "butterfly-like" conformation, analogously to other NNRTIs. In particular, the plausible pharmacophoric elements for TBZs were found to be the benzene fused ring, the aryl group at C-1, and the nitrogen atom of the thiazole nucleus. Using the thiazolobenzimidazole system as a scaffold, they designed 2, 3-diaryl-1, 3-thiazolidin-4-one derivatives as new NNRTIs. The opening of the imidazole nucleus allowed us to keep the main molecular determinants responsible for potent enzyme inhibition. To gain more specific information about the mechanism of action of NNRTIs, computational methods have been used to map the drug-enzyme interaction zones and to identify the correct binding mode of this new class of antiviral agents. A preliminary account of these results has been reported [70].

Structure of TBZ Derivatives



2

Thiazolidin-4-ones are important compounds due to their broad range of biological activities [71-77]. Overviews of their synthesis, properties, reactions and applications have been published [78-79]. 2-Imino-thiazolidin-4-ones have been found to have antifungal activity [80-82], and a convenient method for synthesis involves the reaction of 2-haloacetamides with potassium thiocyanate to produce 2-imino-thiazolidin-4-ones. The R-*N* group at the 3-position of thiazolidin-4-ones may be varied to be alkyl, aryl, heterocyclic groups etc. It is also well known that the thiazole moiety can be important for significant biological activity [83-86]. Chemical alteration of bioactive component is one of the most common approaches in drug discovery with enhanced therapeutic effect [87] and the wide incidence of the heterocyclics moieties in bioactive natural products and pharmaceuticals has made them as central synthetic targets. Small ring containing hetereocyclics atoms like nitrogen, sulfur and oxygen have been under investigation for a long time because of their vital medicinal possessions and also gave to the society from biological and industrial point which helps to understand life processes [88]. They were also accounted as novel inhibitors of the Mur B enzyme, integral component in bacterial peptidoglycan biosynthesis, at the low micro molar level [89]. In recent times, 2-aryl-4-thiazolidinone has been synthesized and found to display potent selective anti-platelet activating 538 factors both in vitro and in vivo and anti inflammatory [90], antibacterial [91], anticancer [92] and anti- HIV-1 activities [93]. Spiro heterocyclic compounds together with thiazolidine moiety have antimicrobial activity [94]. Both pyrazolothiazole and thiazolopyrimidine moieties have effective kinase modulators [95] and are used in pharmaceutical compositions [96]. The second compound has analgesic and anti-Parkinson activities [97] and inhibits the growth of parasite Trypanosoma cruzi [98]. Therefore, such medicinal properties associated with these heterocyclic molecules turn into them as valuable structural units in drug research. These findings encouraged us to synthesize various spiroheterocyclic derivatives of 4-thiazolidinone, for the investigation of an antimicrobial activity profile. From this approach, the purpose of the present communication encompasses the synthesis of series of new compounds having novel spiro cyclohexanonethiazolidine system. Thiazolidinones, which belong to an important group of heterocyclic compounds, have been extensively explored for their application in the field of medicine. Thiazolidinones, with a carbonyl group at position 2(I), 4(II), or 5(III) have been subjects of extensive study in the field of 4-thiazolidinones. Numerous reports have appeared in the literature, which high light their chemistry and use. 4-Thiazolidinone derivatives of thiazolidinone with carbonyl group at 4-position(II) substituent in 2, 3- and 5 position may be varied but the greatest different in structure and

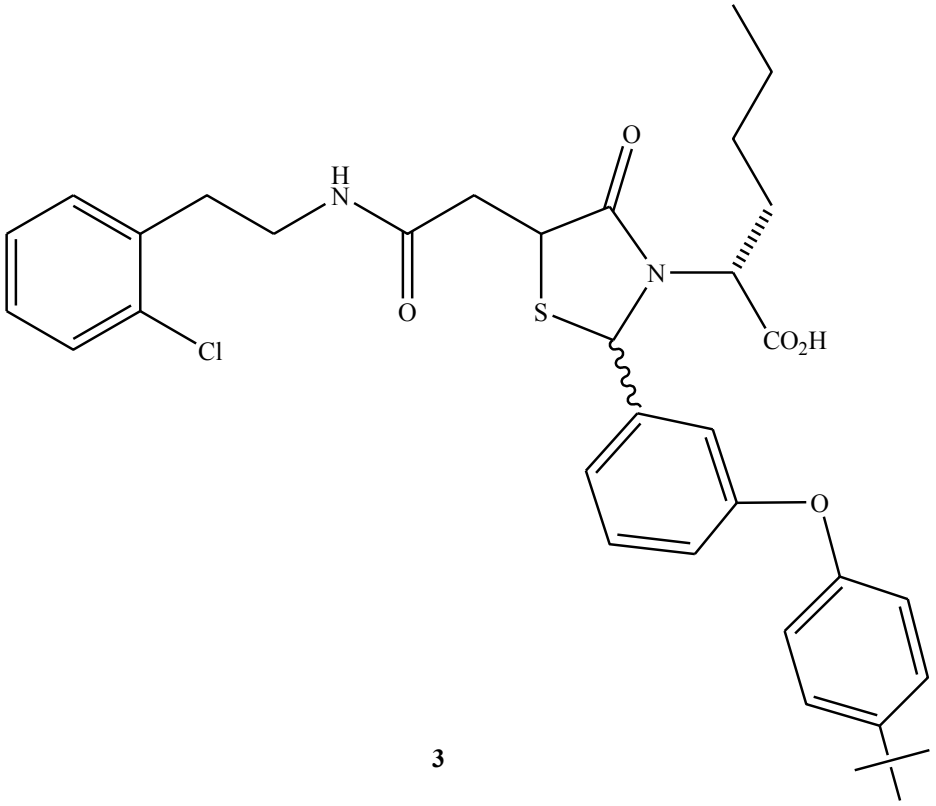
properties is exerted by the group attached to carbon atom at the 2- position and to N atom at the 3-position. 4-Thiazolidinones play a vital role due to their wide range of biological activities and industrial importance. 4-Thiazolidinones are always being an attraction point for researchers because of its efficiency towards various pharmacological usages. The enhanced prevalence of infectious diseases threatens world population. Although tuberculosis appeared as a curable disease for years, it is regaining importance due to the multidrug resistance [99]. Worldwide statistics on tuberculosis surprisingly reveals that, nearly one–third of the world's population is infected with tuberculosis, with approximately eight million new patients every year. A major issue is the increase of multi-drug resistant tuberculosis (MDRTB) giving raises to the disease expensive and incurable especially in immune efficient subjects such as AIDS patients.

Studies of 4-thiazolidinone derivatives

Hence, there is an increased demand to develop new anti-tuberculosis agents effective against pathogens resistant to current treatment. The derivatives of 4-thiazolidinone nucleus have occupied a unique place in the field of medicinal chemistry due to wide range of biological activities like antibacterial, anti-tubercular, anticancer, anticonvulsant and antifungal. They have interesting activity profiles mainly cox-1 inhibitors, inhibitors of bacterial enzyme, non nucleoside inhibitors of HIV Type 1 Reverse Transcriptase (HIVRT) and antihistaminic agents [100]. 4-Thiazolidinones are derivative of thiazolidinone with carbonyl group at the 4th position and formed by the attack of sulphur nucleophile on imine carbon followed by intramolecular cyclisation with elimination of water. Recent studies on molecular modification of the latter 1*H*, 3*H*-thiazolo [3, 4-a] benzimidazoles (TBZs) revealed that, dismantling of the imidazole nucleus leading to the design of new 1, 3-thiazolidin-4-one derivatives, maintained the molecular requirements for enzyme inhibition [101]. According to Andres et al. [102] 4-Thiazolidinones may be considered as phosphate bioisosteres and therefore, inhibit the bacterial enzyme MurB, which is involved in the biosynthesis of peptidoglycan layer of the cell wall. In addition, some thiazolidinones were recently reported as novel inhibitors of mycobacterial rhamnose synthetic enzymes [103]. This new approach is believed to be selective as rhamnose, which is not found in humans has been shown to be essential for mycobacterial cell wall synthesis. Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the oldest and most widely used groups of drugs today [104] . There are more than 20 original mono component NSAIDs, about 200 generics and a significant number of combined drugs and their generic versions at the Ukrainian pharmaceutical

market [105]. However, the problem of searching and creating new NSAIDs remains open, primarily to eliminate gastrointestinal, cardiovascular and renovascular risks in their long-term use [106-108] . Drugs affect the cellular metabolism of arachidonic acid, which is a substrate for the synthesis of active intracellular intermediates, eicosanoids, leukotrienes and others, and is the key mechanism for therapeutic and adverse effects of different classes of NSAIDs [109] . Organic compounds from different classes [110-112] , including 4-thiazolidinone derivatives [113-116], can change the phospholipase A2 activity blocking the process of arachidonic acid releasing from cell membranes phospholipids; selective and non-selective inhibit cyclooxygenases types 1 and 2 (COX-1 and COX-2) and thus prevent the arachidonic acid transformation to eicosanoids; inhibit 5-lipoxygenase (5-LOX) preventing the arachidonic acid conversion to leukotrienes; demonstrate multi activity against the enzyme systems (COX-2/5-LOX dual inhibitors), etc. According to the modern concepts PPAR-receptors play an important role in the cellular mechanisms of inflammatory processes [117]. It is known that 4-thiazolidinones are "classic" high affinity legends' for PPARγ-receptors [118] .The systematic research in the field of potential NSAIDs synthesis and screening among 4-thiazolidinone derivatives is the priority direction for the research group of the Department of Pharmaceutical, Organic and Bioorganic Chemistry at Danylo Halytsky Lviv National Medical University [119-124]. The qualitative and quantitative "structure – anti-inflammatory activity" databases obtained for 4-thiazolidinones allow to carry out the rational structural design of the 4-thiazolidinone "core" for searching new potential NSAIDs. The aim of this research was the synthesis of 5-ylidene-4-thiazolidinones from 2-(4-R-2-formylphenoxy)-N-(R'-phenyl) acetamides, as well as the study of their anti-exudative activity and acute toxicity. Resistance of pathogenic bacteria to available antibiotics is quickly becoming a major problem in the community and hospital based healthcare settings. The search for novel agents to combat resistant bacteria has become one of the most important areas of antibacterial research today [125]. Recently reported that substituted thiazolidinones inhibit the MurB enzyme, integral component in bacterial peptidoglycan biosynthesis, at the low micromolar level [126-127]. Mercaptoimidazole derivatives have also

been reported to show bactericidal and fungucidal activity [128-129] .



3

Structure of enzyme inhibitor (IC_{50}=12 µM) MurB

In view of the above considerations and in continuation of their previous work on imidazoles, thiosemicarbazides and thiazolidinones of pharmaceutical interest [130-131], they report here on the synthesis, characterization and antimicrobial evaluation of new 1-(4,5-diphenyl-1*H*-imidazole-2-yl)mercaptoacetyl-4-alkyl/aryl-3-thiosemicarbazides and 2-[(4,5-diphenyl-1*H*-imidazole-2-yl)mercaptoacetyl]hydrazone-3-alkyl/aryl-4-thiazolidinones derivatives featuring a imidazole nucleus.

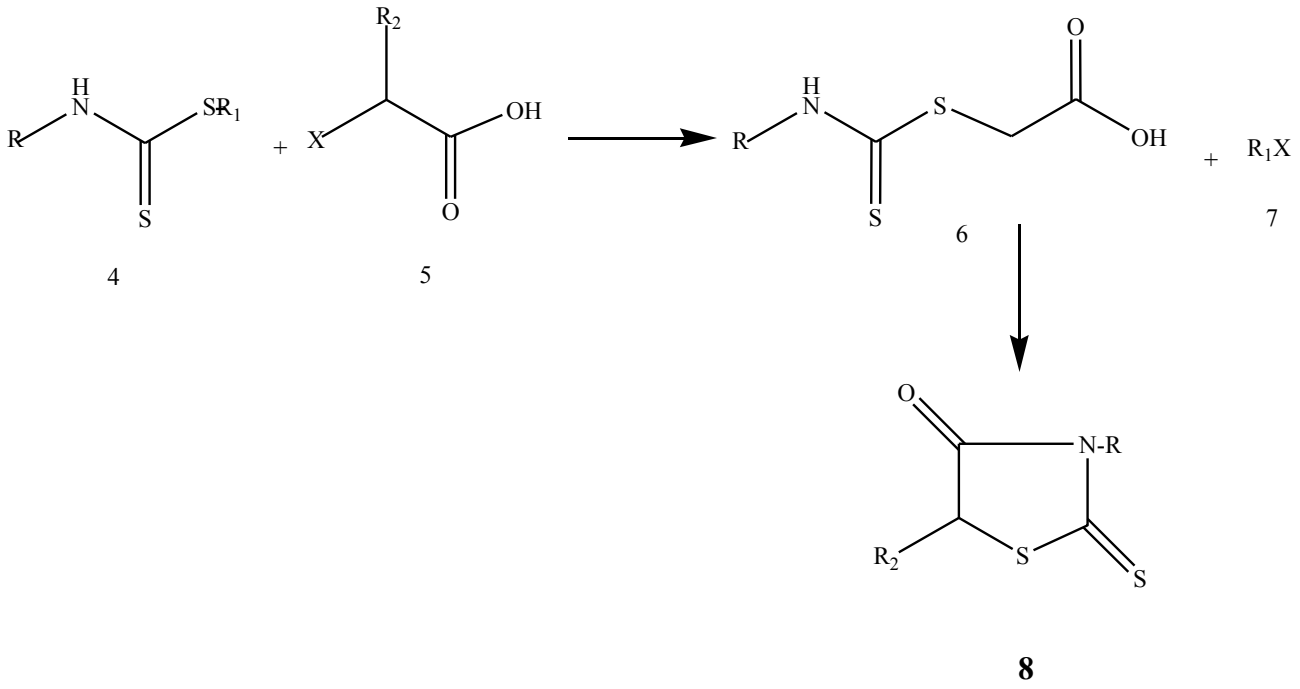
Physical Properties:

The 3-unsubstituted 4-thiazolidinones are usually solids, often melt with decomposition, but the attachment of an alkyl group to the nitrogen lowers the melting point. The 4-thiazolidinones that do not contain aryl or higher alkyl substituents are somewhat soluble in water. Considerable confusion concerning the structure of 4-thiazolidinones exists in the early literature and noncyclic formulas were at first proposed for pseudothiohydantoin and for rhodanine [132]. 4-Thiazolidinones are derivatives of thiazolidine with a carbonyl group at the 4 position [133]. Substitution is possible at 2, 3 and 5 position. Various optical and geometrical isomers are

reported in the references [134]. A series of regioselective isomers has been reported in some works [135, 136]. The carbonyl group of 4- thiazolidinone is highly unreactive. But in few cases 4-thiazolidinone on reaction with Lawesson's reagent gives corresponding 4-thione derivatives [137]. A detail study of tautomerism in 2- imnothiazolidine-4-one has been done by *Akerblom E.* [138].

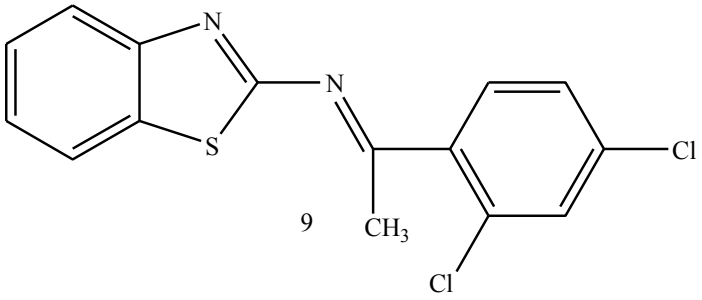
Syntheses of 4-thiazolidinones:

Several methods for syntheses are available in literature which involves conventional one pot, two pot synthesis [139,140] and microwave as well as combinatorial syntheses methods. The dithiocarbamates formed by the reaction of primary amine with carbon disulfide in the presence of base react with haloalkanoic acid in the presence of $NaHCO_3$ to give substituted 2-thiono-4-thiazolidinones as presented in the bellow.



The synthesis of 2-imino-4-thiazolidinones has been reported by using thiourea and sodium salt of labeled monochloroacetic acid [141]. Another method of synthesis of 4- thiazolidinones is by use of thiocyanate, alkyl isothiocyanate with hydrazide/ acetamide followed by the treatment with ethyl bromoacetate and sodium acetate [142]. Schiff's bases obtained by the condensation of ketones and amines also react with mercaptoacetic acid to give 2, 2-disubstituted-4-thiazolidinones [143]. Desai KR *et al* [144] has carried out the microwave assisted synthesis of thiazolidinone from the Schiff's bases by using thiolactic acid. The products were synthesized by

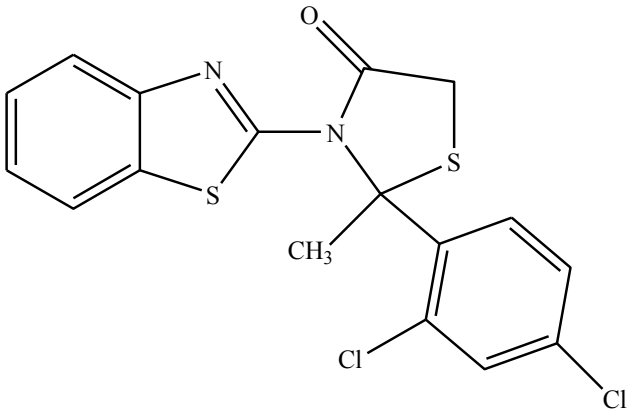
conventional and microwave synthesis and the yield were compared with each other. They concluded that the percent yield with the microwave irradiated synthesis was better than the conventional.



Conventional 15-16 hr

Microwave 6-7 min

SHCH(CH_3)COOH



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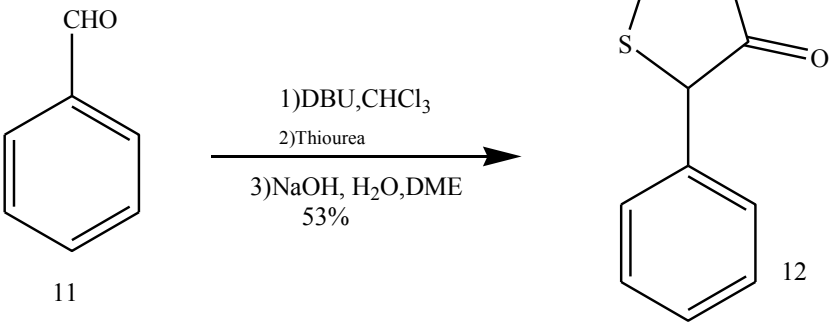


Attempt to synthesize combinatorial libraries of 4-thiazolidinones are present in the literature as reported by *Look GC et al* [145]. HPLC and Mass spectroscopic analysis were done for checking the purity and assure the quality derivatives [146]. Recently library of more than 42,000 compounds were synthesized by encoding 4- thiazolidinone library on solid phase. Three sets of 35 building blocks were combined by encoded split-pool synthesis to give a series of compounds [147]. One pot three component synthesis containing aldehyde, thiourea and chloroform to give 2-amino- 4-thiazolidinone derivatives was also reported [148]. Various imino thiazolidinones were developed by using different reagents with different reaction conditions.

Use of task specific ionic liquid as synthetic equivalent of ionic liquid phase matrices for the synthesis of small library of 4-thiazolidinone is also possible. Ethylene glycol is functionalized in good yields with 4- (formylphenoxy) butyric acid by using DCC/ DMAP catalyst. The synthesis was performed by one pot three component condensations under microwave dielectric heating [149,150]. Lot of work has been done on the microwave dielectric heating based techniques either one step three components or two step processes [151-155]. Microwave method is the easiest and rapid method of synthesis. The yield of product obtained was better than the conventional technique. Generally environmentally benign catalysts were used for the synthesis which helps in the less pollution and lower wastage of the reagents.

Spectral study

Ultra violet spectra The U. V. spectral study in tabular form was present in earlier literature Reviews [132,138]. The ultraviolet absorption spectra of a series of 2-(arylimino)-4 thiazolidinones containing electron donor and electron acceptor substituent's in the phenyl ring were studied [156]. When substituents are present in the paraposition of the phenyl ring, the position of characteristic thione absorption is shifted. UV spectra of the 5-arylazo derivatives of thiazolidin-4-one 5-phenylazo-2-phenyliminothiazolidin-4-one were synthesized in the literature [157]. The displacement of the absorption maximum of the N=N group to the long wave part of the spectrum by 42 nm in the spectrum of 5-arylazo derivative of substituted compound caused by the presence of a nitro group in the chain of conjugated double bonds with the azo group is a confirmation of the existence of the compound in the azo form.

Infrared Spectra

The infrared spectra of 4-thiazolidinones are helpful in determining the structure of the compounds. It is also useful in the determination of configuration of *cis* and *trans* isomers [158]. The *cis* isomer is favored when H-bonding is otherwise impossible. In other circumstances the *trans* isomer is the stable form [159]. The carbonyl peak [160] in the 2-alkyl-4- thiazolidinone was somewhere around 1680-1740 cm^{-1}, Characteristic N-H stretching1 was in the range of 3100-3400 cm^{-1}.

NMR spectra

Both ^{1}H and ^{13}C NMR are important so as to confirm the structure of the derivatives and are also useful in regioselective synthesis of isomers. Some articles describe ^{1}H-NMR spectroscopic study as a method to distinguish between the intermolecular and intramolecular hydrogen bonding in (Z)-2-(5-ethoxycarbonylmethyl-4-oxothiazolidin-2-ylidene)-1-phenylethanone, being an example of the thiazolidinone series [161]. Ferrocenyl-thiosemicarbazones and their S-methylated derivatives can be used for the synthesis of a variety of novel ferrocenyl-substituted S,N- and N,N-heterocycles the intermolecular S–O and S–N close contact interactions seem to be governing factors in the cyclization reactions of thiosemicarbazone-reagents which is described with the help of ^{13}C and ^{1}H NMR [162]. A series of substituted 4-thiazolidinones in $CDCl_3$ were synthesized. The chemical shift and C, H spin coupling constants are given [163].

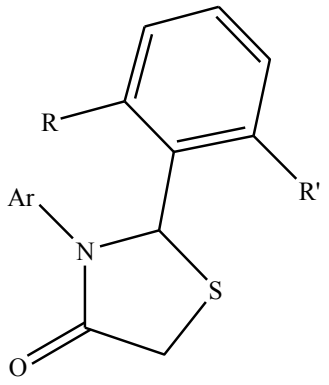
Mass Spectra

The molecular ion peaks in the mass spectrum of 2-imno-4-oxothiazolidinyl-5-acetatehave been assigned [164]. Various spirothiazolidinones and fatty acid chain-substituted thiazolidinones were synthesized and characterized. In contrast to spirothiazolidinones in which the parent peaks usually are the base peak, fatty acid chain-substituted thiazolidinones showed very low intensity M^{+} peaks two significant peaks m/z 42 and 43, of comparatively moderate intensity are also observed in the spectra of all the three thiazolidinone [165]. N-tryptophyl-4-thiazolidinones and Ntryptophyl-5-benzylidene-4-thiazolidinones were synthesized and possible fragmentation patterns of these compounds by electron impact mass spectrometry was reported [166]. All compounds have shown the same base peak at m/z 143.

Pharmacological uses of 4-thiazolidinones

Anti-HIV activity

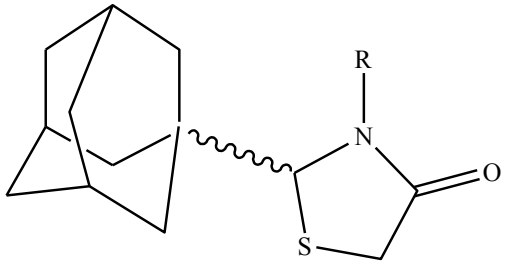
The anti-HIV activity of several series of 2, 3-diaryl-1, 3-thiazolidin-4-ones has been studied. Which are reported as a new family of antiviral agents acting as NNRTIs with minimal cytotoxicity [167-169].



13

2,3-diaryl-1,3-thiazolidin-4-ones

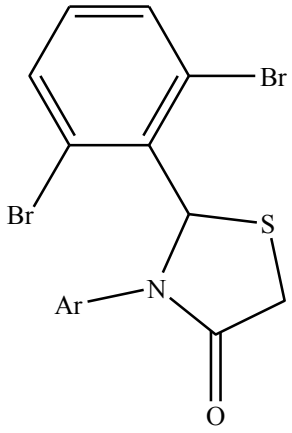
2-adamantyl-substituted thiazolidin-4-ones were synthesized and evaluated for activity against HIV-1 (IIIB) and HIV-2(ROD) in CEM cell cultures, by taking Nevirapine as reference compounds [170].



14

2-adamantyl-substituted thiazolidin-4-ones as Anti-HIV agent

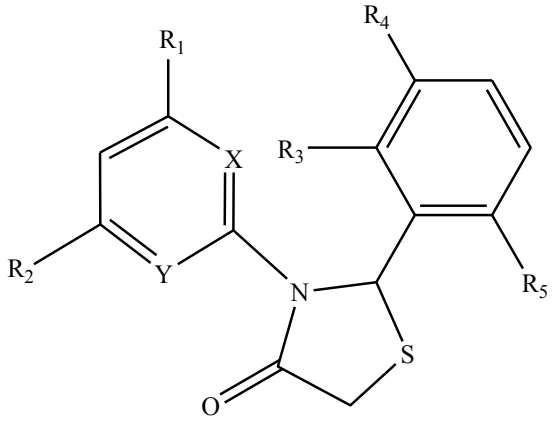
Some researchers reported 2-(2, 6-dibromophenyl)-3-heteroaryl-1, 3-thiazolidin-4-one derivatives as shown in the compound (15). A positive correlation between size of the halogen substituent and HIV-RT inhibitory activity was taken as logic for the synthesis [171].



15

2-(2, 6-dibromophenyl)-3-heteroaryl-1, 3-thiazolidin-4-one derivatives

Microwave-assisted synthesis of 2, 3- diaryl-1, 3-thiazolidin-4-ones was performed in order to achieve striking reductions in reaction times, better yields, cleaner reactions [172].



16

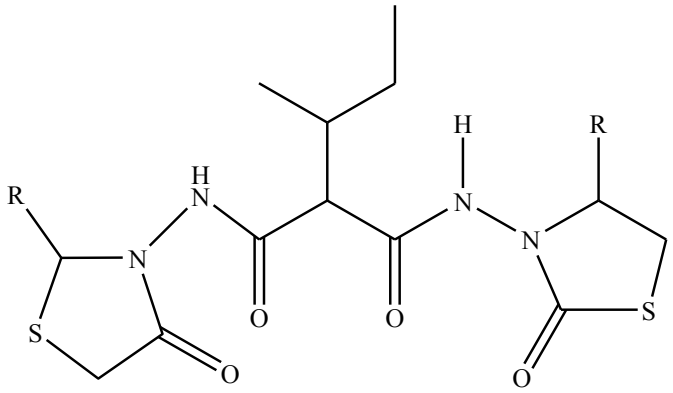
Microwave-assisted synthesis of 2, 3-diaryl-1, 3-thiazolidin-4-ones

Recently prediction of Anti-HIV activity of 1, 3, 4-thiazolidinone derivatives were made on the basis of QSAR. CoMFA and CoMSIA were the two models used for the analysis. Based on the structures and biodata of previous thiazolidinone analogs, 3D-QSAR studies have been performed with a training set consisting of 96 molecules [173].

Anticonvulsant activity

Number of articles were found for the anticonvulsant potential of 4- thiazolidinones where substitution on 2, 3, 5 positions were done. Most of the compounds were found to exhibit protection against pentylenetetrazole induced seizures [174-179]. Researchers reported the synthesis, characterization, and anticonvulsant evaluation of new N,N'-bis(arylidene) dihydrazide

and bis*(4*-thiazolidinone) derivatives. Up to 90% protection was observed in the pentylenetetrazole seizure [180].



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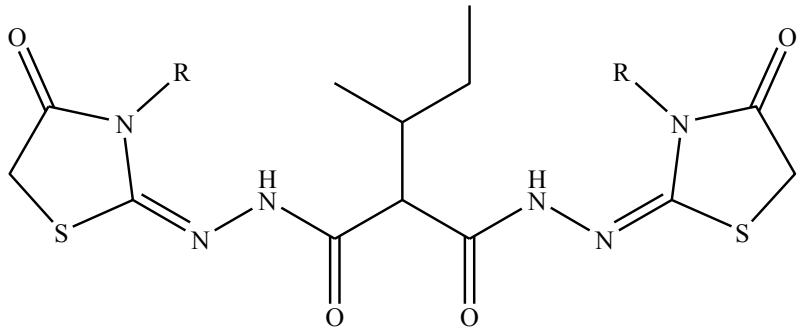
N,N'-bis(arylidene)dihydrazide

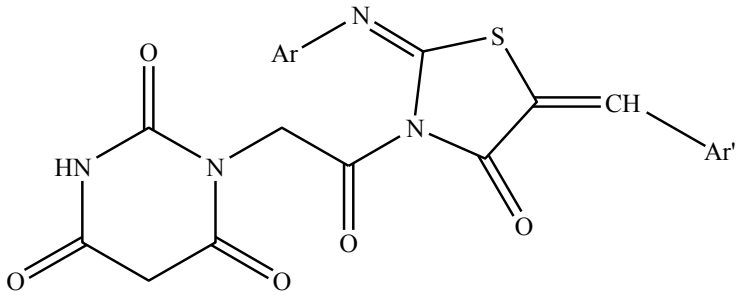


18

Bis*(4*-thiazolidinone)

Synthesis of newer thiadiazolyl and thiazolidinonyl quinazolin-4(3H)-ones was done in 2002 by Archana, kumar A [181]. The compounds were screened for their anticonvulsant activity and were compared with the standard drugs, phenytoin sodium, lamotrigine and sodium valproate. Out of the 30 compounds the most active compound was 3-({4-[2-(m-methoxy-hydroxyphenyl) -4-oxo-1, 3-thiazolidin-3-yl]-1, 3, 4-thiadiazol- 2-yl}-methylamino)-2-methyl-6-bromoquinazolin-4(3H)-one. Recently anticonvulsant activity of clubbed Thiazolidinone-barbituric acid and thiazolidinone-triazole derivatives have been reported [182]. The compound in, substituted with different phenylthiazolidinonyl amino moieties at the 5 position of barbituric acid, has shown varying degrees of anticonvulsant activity. While 3-(2-chloroacetyl)-2-arylimino-5-[(*Z*)-arylmethylidene]-1, 3- thiazolan-4-ones on treatment with 5-(1- phenoxyethyl)-

4H-1, 2, 4-triazole-3-thiol in identical conditions provided a set of bulkier derivatives which have also shown the anticonvulsant potential.



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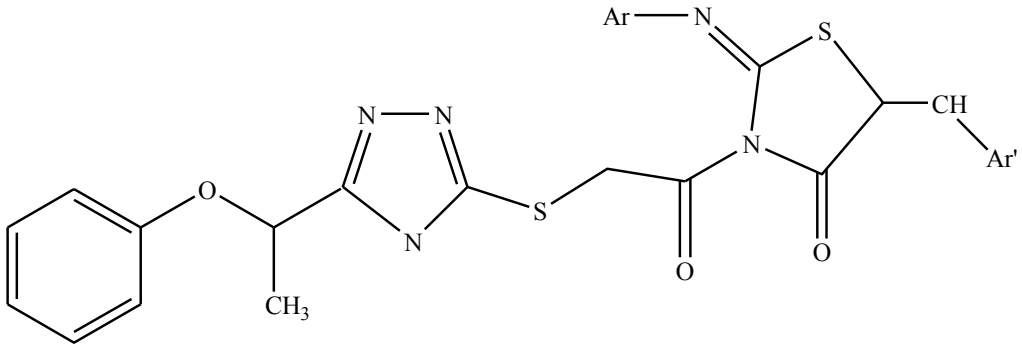
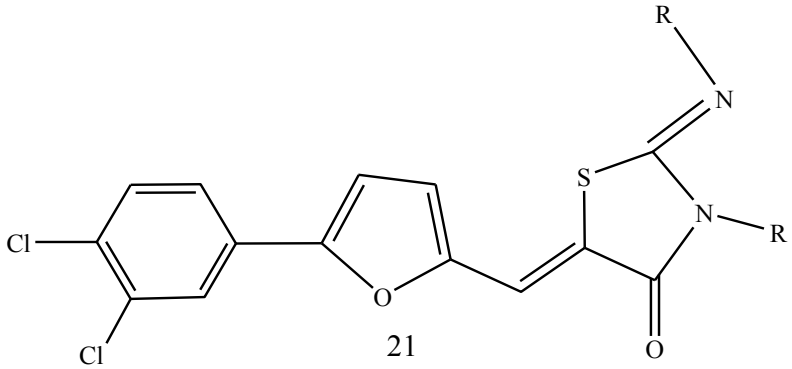


20

Antimicrobial activity

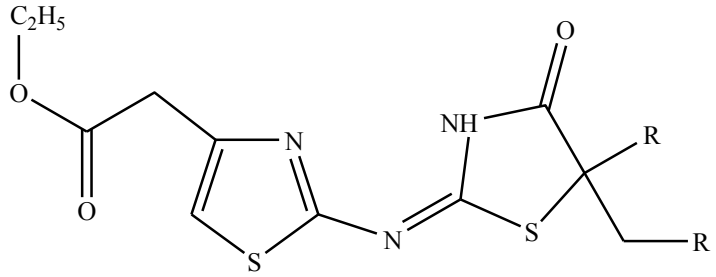
2-(ptolylimino)-3-(4-tolyl)-5-[5-(3,4-dichlorophenyl)-2-furylidene]-4-thiazolidinone and derivatives as an antimicrobial agents were screened *in vitro* for their antimicrobial activity towards variety of bacterial strains such as *B. mega, S. aureus, E. coli, P. vulgaris* and *fungi* such as *Aspergillus niger* at a concentration of 40 g/L and in conclusion remarkable inhibition were observed in compounds bearing R=phenyl, 2-methoxyphenyl, 2-methylphenyl, 3-methylphenyl 4-nitrophenyl substituents [183].



21

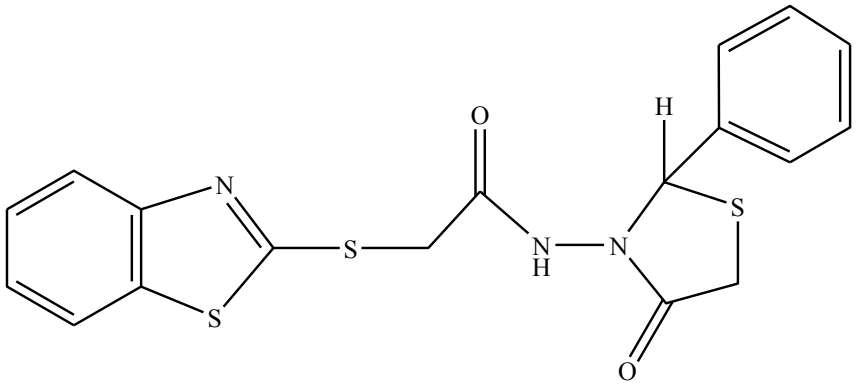
2-(p-tolylimino)-3-(4-tolyl)-5-[5-(3, 4-dichlorophenyl)-2-furylidene]-4-thiazolidinone

Various 5-substituted 5-(N, N-disubstituted aminomethyl)-2-[(4-carbethoxymethylthiazol-2-yl)imino]-4-thiazolidinones were screened for their in vitro antibacterial activity against *Staphylococcus aureus* ATCC 6538, *Staphylococcus epidermidis* ATCC 12228, *Escherichia coli* ATCC 8739, *Klebsiella pneumoniae* ATCC 4352, *Pseudomonas aeruginosa* ATCC 1539, *Salmonella typhi*, *Shigella flexneri* and *Proteus mirabilis* ATCC 14153 using disk diffusion [184].



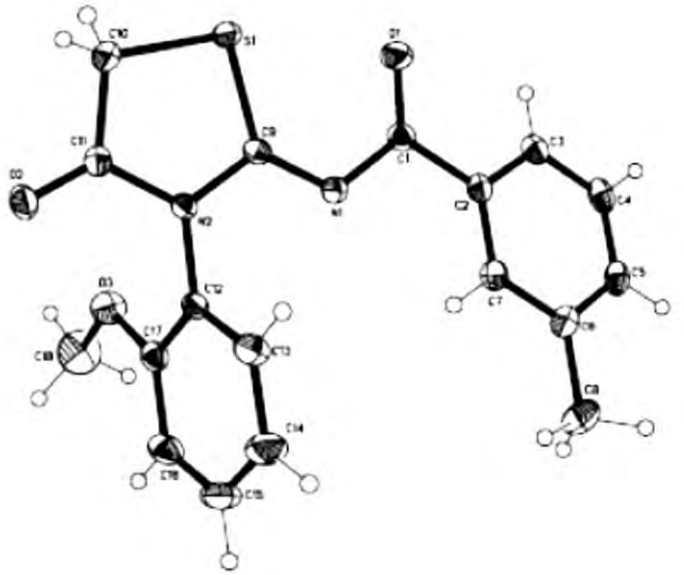
22

Desai, K. G. and Desai, K. R. have synthesized five membered sulfur containing heterocyclic derivatives 2-(aryl)-3-[2-(benzothiazolylthio)- acetamidyl]-4-oxo-thiazolidines. All the compounds have been screened for their antibacterial activity against *Escherchia coli* (Gram^{-ve}), *Staphylococcus aureus* and *Bacillus substilis* (Gram^{+ve}) [185].



23

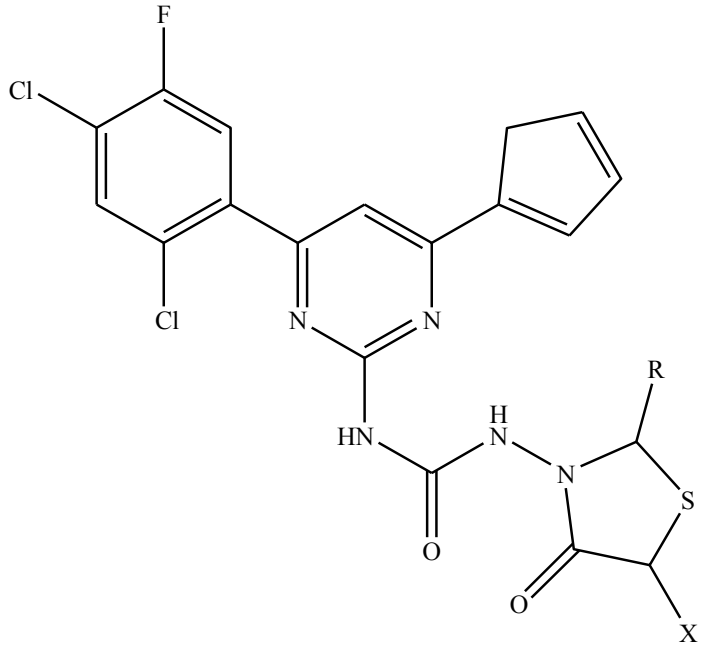
Several derivatives of 2-aroylimino-3-arylthiazolidin-4-ones were prepared and were screened for antimicrobial activity by Saeed A [186]. The compounds were characterized by spectroscopic techniques and molecular structure is shown in the following figure.



24

Molecular structure of 2-aroylimino-3-arylthiazolidin-4-ones

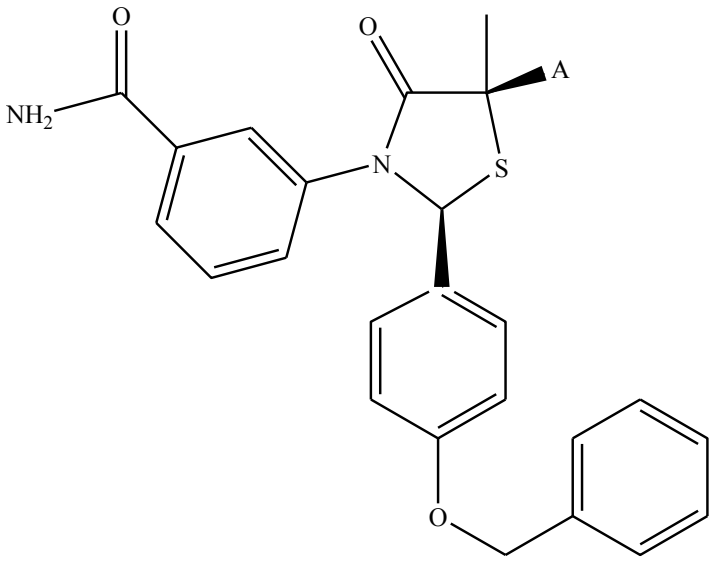
A series of 2-(substituted phenyl)-3-[4- (2, 4-dichloro-5-fluorophenyl)-6- (2-thienyl) pyrimidine-2-yl-ureido]-5*H*/ methyl/carboxymethyl-4-thiazolidinones were prepared. All the derivatives were screened for antibacterial activity [187]. Number of other researchers also synthesized and screened 4-thiazolidinone derivatives for antimicrobial potential [188-194].



25

Follicle stimulating hormone (FSH) receptor agonist activity

Follicle stimulating hormone (FSH) is a 38 kDa protein that triggers maturation of ovarian follicles in women and spermatogenesis in men. It is released from the anterior pituitary gland, following stimulation by gonadotropin releasing hormone (GnRH), and serves as the naturally occurring agonist of the FSH receptor. *Yanofsky* have shown the allosteric activation of FSH receptor, by screening unbiased combinatorial chemistry libraries of thiazolidinone derivatives (Fig), using a cAMP responsive luciferase reporter assay [195]. They also have shown that discrete modifications in the chemical structure of the thiazolidinone agonists produced compounds with different pharmacological properties [196]. This was done by preparing substituted 5-alkyl [197], Gama lactam substituted [198] 4- thiazolidinone derivatives.

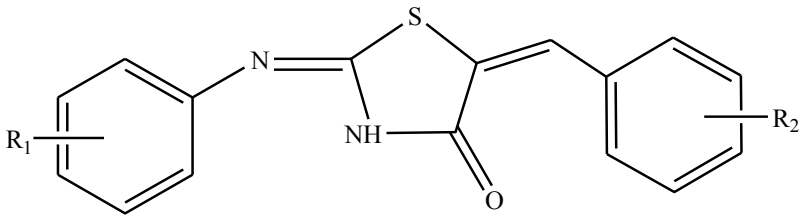


26

Maclean *et al.* reported the FSH agonist activity of an encoded 4-thiazolidinone library [199]. Among the hits discovered in these studies was compound 2-chloro-4- [5-{[2-(3H-inden-1-yl)-ethylcarbamoyl] -methyl}-2-(4-methixyphenyl)-4-oxothiazolidin- 3-yl]-benzamide, which possessed moderate FSH receptor agonistic activity [200].

Anti cancer activity, antiproliferative activity

Ten cytoselective compounds have been identified from 372 thiazolidinone analogues by applying iterative library approaches. These compounds selectively killed both non-small cell lung cancer cell line H460 and its paclitaxel-resistant variant H460taxR at an IC50 between 0.21 and 2.93M while showing much less toxicity to normal human fibroblasts at concentrations up to 195 M. A pharmacophore derived from active molecules suggested that two hydrogen bond acceptors and three hydrophobic regions were common features [201].

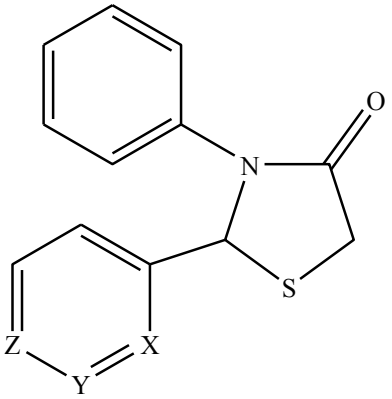


27

Gududuru have synthesized a series of 2-aryl-4-oxothiazolidin-3-yl amides and were evaluated for ability to inhibit prostate cancer cells. Few potent compounds were detected, which were effective in killing prostate cancer cells with improved selectivity compared to serine amide phosphates [202]. Various 4-thiazolidinone derivatives were synthesized for in vitro antiproliferative activity on five cell lines of human colon cancers, obtained from the American type culture collection [203-207]. Thiazolidinone amides, carboxylic acids, serine amides were synthesized and tested for possible anticancer activity [208].

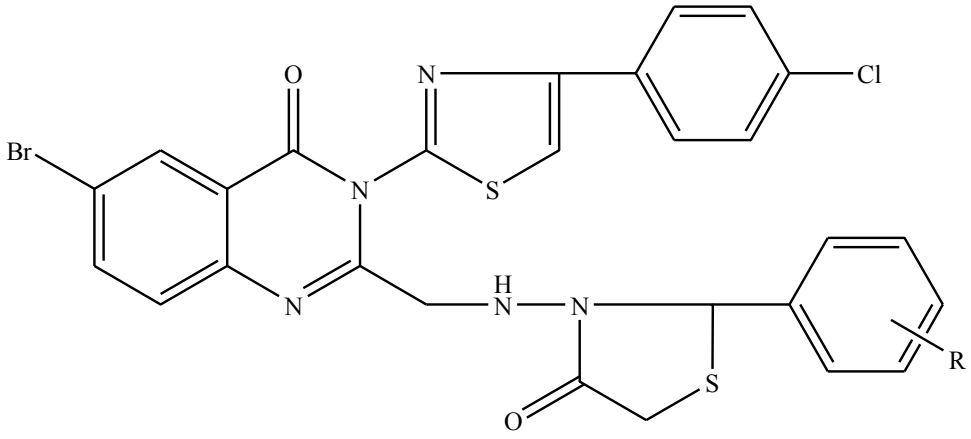
Anti-inflammatory activity

Sparatore F has synthesized aromatic Schiff bases and 2, 3-disubstituted-1, 3- thiazolidin-4-one derivatives as anti-inflammatory agents. Both types of compounds displayed good level of activity against carrageenan induced edema in rat hind paw, while only moderate activity was observed in the writhing test in mice [209].



28

Kumar A have synthesized 3-[4'-(pchlorophenyl)- thiazol-20-yl]-2-[(substituted azetidinone/ thiazolidinone)-aminomethyl] - 6- bromoquinazolin -4- ones . Some of the compounds have shown satisfactory anti-inflammatory activity [210].



29

A series of 4-thiazolidinone compounds, represented by LY178002 (5-[3,5-bis (1,1 dimethylethyl)- 4- hydroxyphenyl] methylene-4- thiazolidinone), have been described as potent inhibitors of cyclooxygenase and 5-1ipoxygenase, also an inhibitor of phospholipase A 2 and cellular production of LTB4 by human polymorphonuclear leukocytes (PMNL). The results indicate that LY178002 is more effective in suppressing bone damage than the edema [211]. Ottana *et al* investigated 3, 3-(1, 2- ethanediyl)-bis[2-aryl-4-thiazolidinone] derivatives, which showed interesting stereo selective anti-inflammatory/ analgesic activities, suggesting that they might preferentially interact with inducible COX-2 isoform [212]. Synthesized 2-imino-4-

thiazolidinones and 5-arylidene- 2-imino-4-thiazolidinones were tested for in vivo anti-inflammatory activity in models of acute inflammation such as carrageenan-induced paw edema and pleurisy assay in rats [213,214]. All derivatives exhibited significant activity levels. In addition, the ability of such a new class of anti-inflammatory agents to inhibit COX isoform was assessed in murine monocyte/ macrophage J774 cell line assay. Newbould studied the anti-inflammatory activity of 2-[(butoxycarbonyl) methylene]-4-thiazolidinone. The compound was found to be devoid of activity against most models of acute inflammation. However it partially inhibited Carageenan induced edema in the rat and prevented completely the development of secondary lesions in the rats injected with adjuvant in the footpad [215]. Geronikaki AA *et* al [216] has performed computer aided discovery of anti-inflammatory potential of 4-thiazolidinones by using PASS (Prediction of Activity Spectra for Substances).

CFTR inhibitor

The cystic fibrosis transmembrane conductance regulator (CFTR) is a cAMP-regulated chloride channel, which when mutated can produce the hereditary disease cystic fibrosis. CFTR inhibition is a potential strategy for therapy of secretary diarrheas [217]. Tonghui Ma [218] has shown that the 4- thiazolidinones also have CFTR inhibitory potential. The purpose of the study was to identify high affinity CFTR inhibitors for application to studies of CF disease mechanisms and to the treatment of secretary diarrheas. The primary screening of 50,000 diverse compounds identified a small set of putative inhibitors of the 2-thioxo-4- thiazolidinone compound classes. These compounds were unrelated structurally to known CFTR activators and to the CFTR inhibitors diphenylamine-2 carboxylate (DPC), 5-nitro-2(3-phenylpropyl-amino) benzoate (NPPB) and glibenclamide. The most potent CFTR inhibitor identified by screening of library of structural analogs had a K1 of about 300nM for inhibition of Cl current in human airway cells. Inhibition was rapid, reversible and voltage dependant. Sonawane ND [219], have synthesized thiazolidinone 3-[(3-trifluoromethyl) phenyl]-5-[(4-carboxyphenyl) methylene] - 2-thioxo-4-thiazolidinone (CFTRinh-172) which inhibits cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel conductance with sub-micromolar affinity and blocks cholera toxin-induced intestinal fluid secretion. Greatest CFTR inhibition potency was found for 3-CF3 and polar group-substituted-phenyl rings, and a thiazolidinone core. Two compounds with CFTR inhibition potency and solubility >180 lM (>10-fold more than CFTRinh-172) were identified:

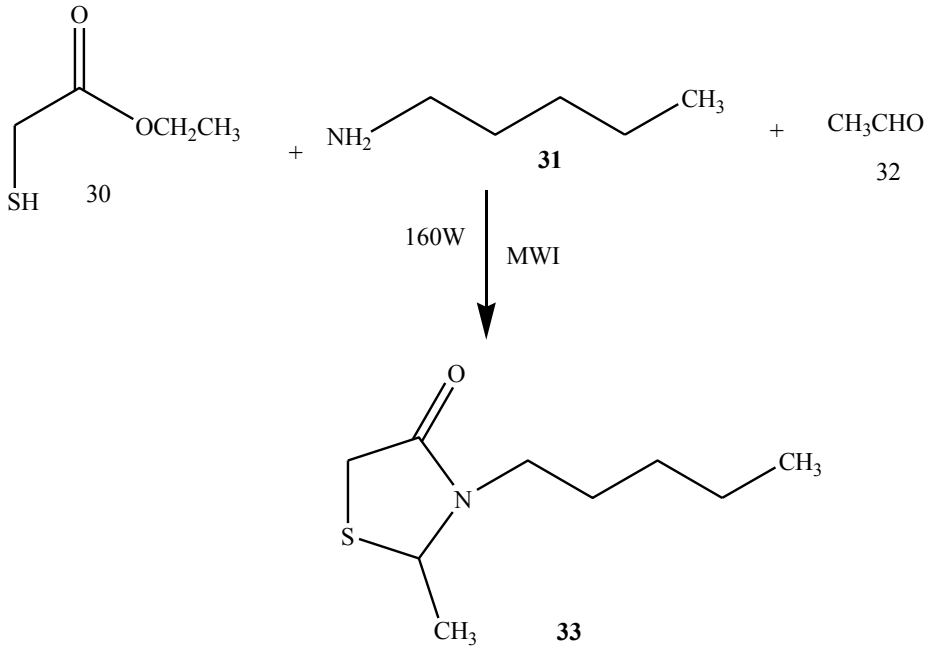
Tetrazolo-172, containing 4-tetrazolophenyl in place of 4-carboxyphenyl, and Oxo 172, containing thiazolidinedione in place of the thiazolidinone core. The same researchers and their co workers have shown the CFTR inhibitory activity of thiazolidinone derivatives using computational as well as conventional methods [220, 221].

Miscellaneous uses

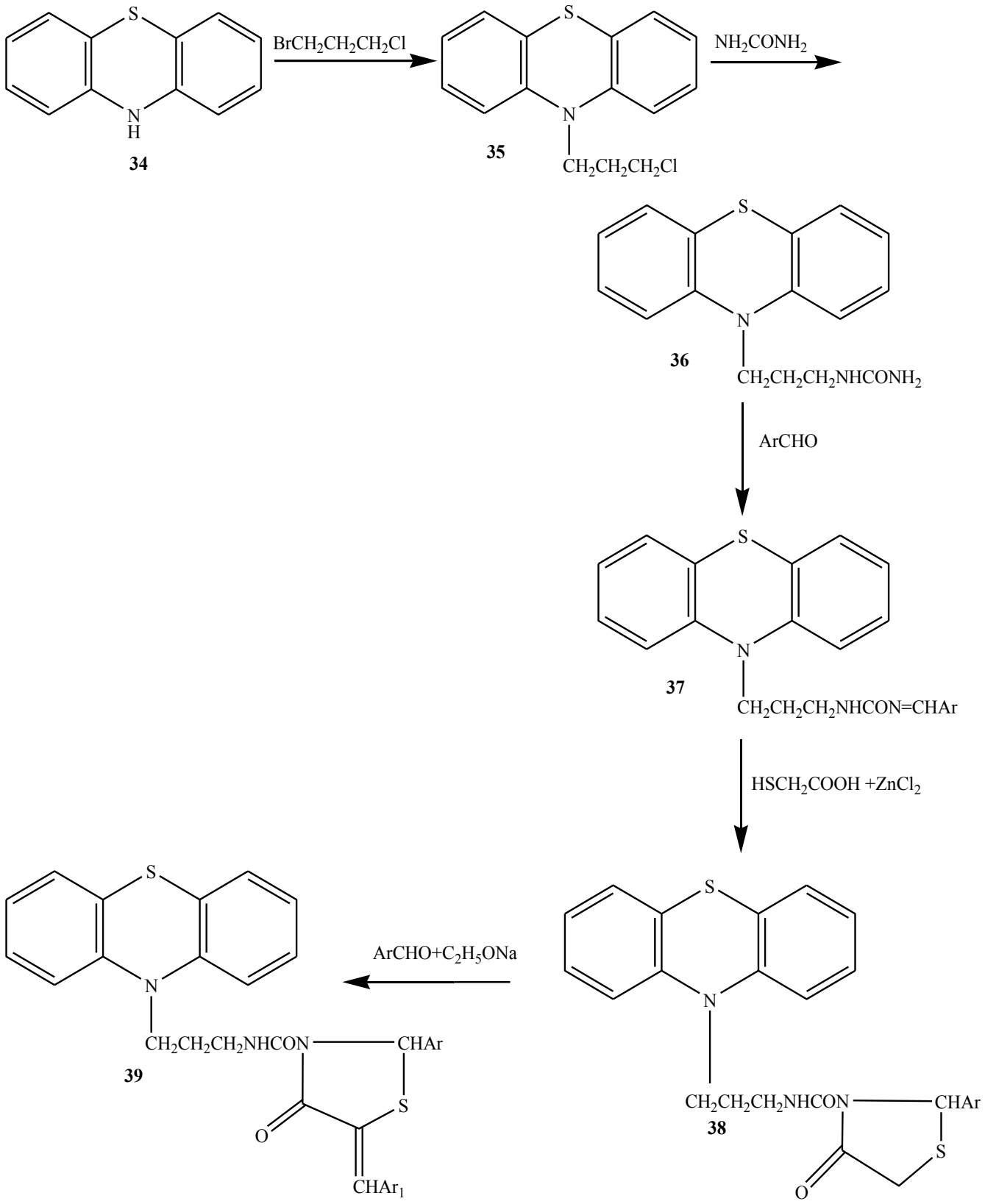
Apart from pharmacological applications the 4-thiazolidinones have also been used in synthesis. One of the most older use was in the synthesis of merocyanine dyes which extend the sensitivity of silver halide emulsions to wavelengths within the visible region of the spectrum. Pawelczyk A and Zaprutko L have synthesized the 4-thiazolidinone derivatives by microwave method as a new fragrant substances and unsaturated analogs of jasmines [222]. The npentylamine was mixed with acetaldehyde. The mixture was stirred at room temperature under condenser. After 1 h ethyl thioglycolate (or thioglycolic acid) was added. Reagents were irradiated for 5 min with 160 W by microwaves in a flask with condenser and further treated with ethyl acetate.

Microwave assisted jasmine analogues.

Thiazolidines have been shown to possess various remarkable biological activities such as



analgesic, amoebicidal, nematocidal, anaesthetic, mosquito- -repellent, anti-HIV, antitubercular, EGFR and HER-2 kinase inhibitor [223], antiproliferative [224, 225] *etc*. Phenothiazine is also a bioactive heterocyclic compound of pharmaceutical importance and possesses different biological activities *viz*. antibacterial [226, 227], antifungal [228], antitubercular [229] and anti-inflammatory [230]. In the present study, compounds **35**, **36**, **37**, **38** and **39** were synthesized from compound **34.** The starting material, phenothiazine with 1-bromo-3-chloropropane underwent a nucleophilic substitution reaction yielding 10-(3-chloropropyl)-10*H*phenothiazine, compound **35**. Compound **35** on reaction with urea afforded *N*-[3- (10*H*-phenothiazin-10-yl) propyl] urea, compound **36**. Compound **36** on reaction with several selected substituted benzaldehydes underwent a condensation reaction to afford *N*-[3-(10*H*-phenothiazin-10-yl) propyl]-*N*'-[(substituted phenyl) - methylidene] urea, compounds **37**. The reaction of thioglycolic acid with compounds **37** in the presence of anhydrous $ZnCl_2$ gave new heterocyclic compounds *N*-[3-(10*H*-phenothiazin-10-yl)propyl]-2-(substituted phenyl)-4-oxo-3-thiazolidinecarboxamide, compounds **38**. Compounds **38** on treatment with various selected substituted benzaldehydes in the presence of C_2H_5ONa underwent a Knoevenagel condensation reaction to yield the final products *N*-[3-(10*H*- -phenothiazin-10-yl)propyl]-2-(substituted phenyl)-4-oxo-5-(substituted benzylidene)- 3-thiazolidine-carboxamide, compounds **38**. The structures of all the newly synthesized compounds **35**, **36**, **37**, **38** and **39** were confirmed by IR, ^{1}H-NMR, ^{13}C-NMR and FAB mass spectroscopy and by chemical analysis. All the above compounds were screened for their antimicrobial activity against some selected bacteria and fungi and antituberculosis activity against *Mycobacterium tuberculosis*.


S
N
H
34
BrCH2CH2CH2Cl
S
N
CH2CH2CH2Cl
35
NH2CONH2
S
N
CH2CH2CH2NHCONH2
36
ArCHO
S
N
CH2CH2CH2NHCON=CHAr
37
HSCH2COOH +ZnCl2
S
N
CH2CH2CH2NHCON
CHAr
S
O
38
ArCHO+C2H5ONa
S
N
CH2CH2CH2NHCON
CHAr
S
O
CHAr1
39

Biological study

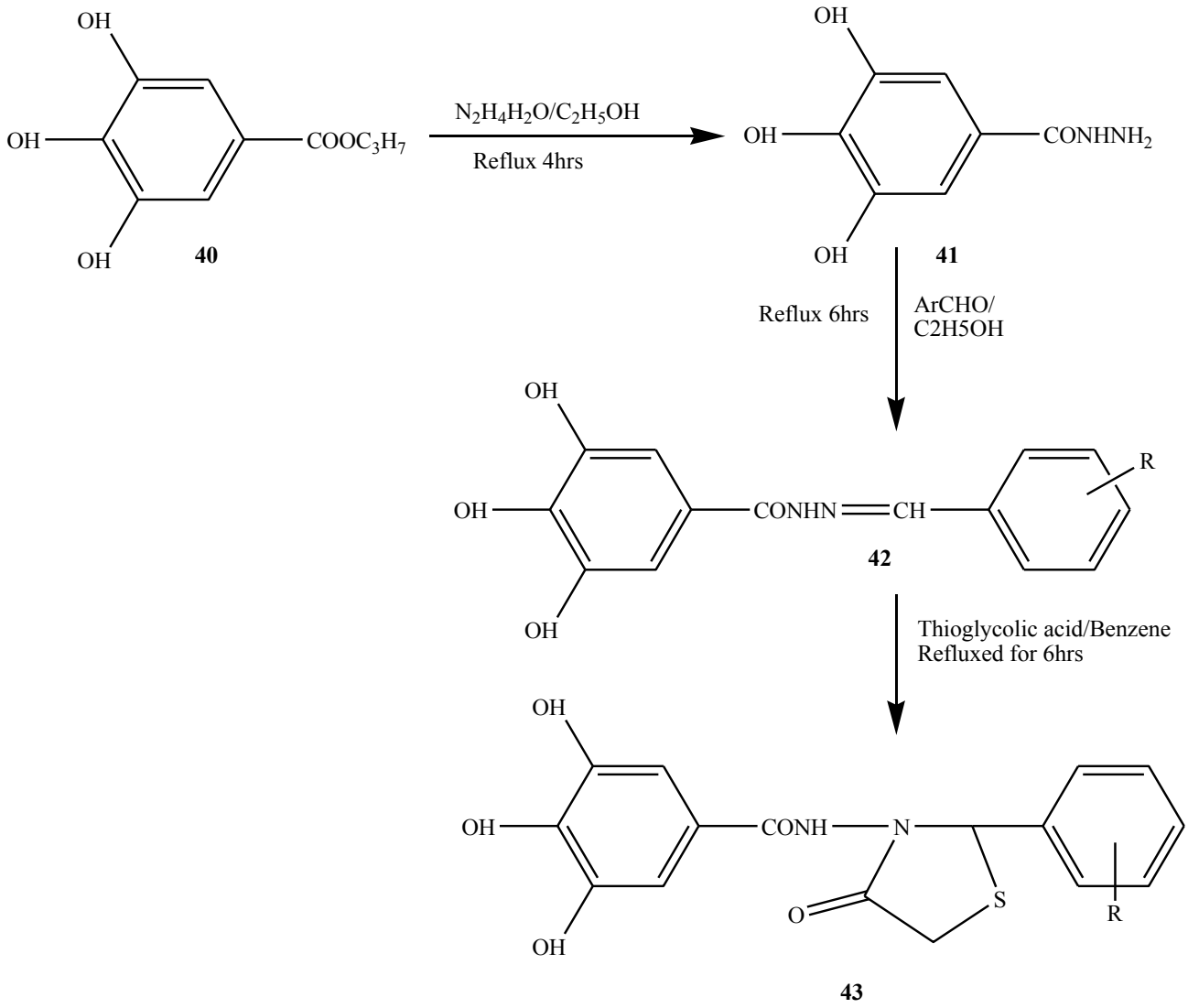
The antibacterial, antifungal and anti-tubercular activities of compounds **35**, **36**, **37**, **38** and **39** were assayed *in vitro* against selected bacteria, *i.e*., *Escherichia coli*, *Bacillus subtilis*, *Staphylococus aureus*, and selected fungi, *Aspergillus flavus*, *Aspergillus niger* and *Candida albicans* H37Rv strain. The inhibition zone (mm) of compounds **35**, **36**, **37**, **38** and **39** were determined using the filter paper disc diffusion method [226-228] (antibacterial and antifungal activity) at two concentration of 50 and 100 ppm and the percentage activity of compounds **35**,**36**, **37**, **38** and **39** were determined using the L. J. medium (conventional) method (antitubercular activity) at 25 and 50 μg mL-1 and lower concentrations. Streptomycin and griseofulvin were used as the standard for the antibacterial and antifungal activity, respectively, and for the antitubercular activity, isoniazid and rifampicin were taken as standards. Tuberculosis (TB) is one of the most common infections caused by *Mycobacterium tuberculosis*.

According to the World Health Organization (WHO), nearly 2 billion people, i.e. one third of the world's population have been exposed to the tuberculosis pathogen [231]. Annually, 8 million people become ill with tuberculosis [232]. The association of tuberculosis and HIV infections is so dramatic that in some cases, nearly two- third of the patients diagnosed with the tuberculosis are also HIV- seropositive [233]. There have been no new classes of TB drugs in 40 years. Isoniazid continues to be the drug of choice for TB [234]. Moreover there has been a recent and disturbing increase in the number of TB cases that are caused by organisms which are resistant to the first-line drugs such as Isoniazid, Rifampicin, Ethambutol, Streptomycin and Pyrazinamide [235]. On September 1, 2006, WHO announced that a deadly new strain of extensively drug resistant tuberculosis (XDR-TB) had been detected in Tugela Ferry, a rural town in the South African province of KwaZulu-Natal, the epicenter of South Africa's HIV/AIDS epidemic. Of the 544 patients studied in the area in 2005, 221 had multi-drug-resistant tuberculosis (MDR-TB). Of these 221 cases, 53 were identified as XDR-TB [236], i.e., MDR-TB plus resistance to at least three of the six classes of secondline agents [237]. The Global Alliance for TB Drug Development (GATB) was established to address this need [238]. Its top priority is the development of new agents that will shorten the duration of chemotherapy from the current 6–8 months to two months or less, although new drugs with activity against multidrug resistant tuberculosis and latent TB are also needed. Gallic acid is a naturally occurring antioxidant. It

occurs along with tannins. It possesses various biological activities like analgesic [239], antineoplastic [240], anti-proliferative [241] and anti-inflammatory [242]. Keeping this in mind, a large number of gallic acid derivatives were prepared in our laboratory and screened for antimycotic activity.

Antitubercular activity

Antitubercular activity was evaluated against *Mycobacterium tuberculosis* H37 Rv ATCC27294 using well known Microplate Alamar Blue Assay method. Antitubercular susceptibility testing was performed in black, clear-bottomed, 96-well microplates (black view plates; Packard Instrument Company, Meriden) in order to minimize background fluorescence. Initial drug dilutions were prepared in dimethylsulfoxide, and subsequent two fold dilutions were performed in 0.1 ml of 7H9GC media in the microplates. 100ml of 2000CFU/ml of *Mycobacterium tuberculosis* H37 Rv in 7H9GC were added to each well of 96 well microtitre plate containing test compounds. Three control well plates containing drug and medium, bacteria and medium and medium only were prepared and microtitre plates were incubated at 37°C. At day 7 of incubation Alamar Blue dye solution (20 µl Alamar Blue solution and12.5 ml of 20% Tween 80) were added to all the wells and plates were re-incubated at 37 °C for 24 hours. Fluorescence was measured in a Victor II multilabel fluorometer (Perkin Elmer Life Sciences Inc., Boston) and MIC was determined.



Synthesis of novel thiazolidinone of Gallic acid

Tuberculosis (TB) remains as a major global health problem. It causes ill-health among millions of people each year and ranks as the second leading cause of death from an infectious disease worldwide, after the human immune deficiency virus (HIV). The latest estimates included in WHO's report are; there were almost 9 million new cases and 1.4 million TB deaths in 2012(990 000 among HIV negative people and 430 000 HIV-associated TB deaths). Short-course regimens of first-line drugs that can cure around 90% of cases have been available since the 1980s. The World Health Organization (WHO) declared TB a global public health emergency in 1993. Starting in the mid-1990s, efforts to improve TB care and control intensified at national and

international levels. Globally, 3.7% of new cases and 20% of previously treated cases are estimated to have MDR-TB. In 2010, the treatment success rate was 85% among all new TB cases and 87% among new cases of sputum smear-positive pulmonary TB (the most infectious cases). Improvement in treatment outcomes is needed in the European Region, where the treatment success rate in 2010 was 74% and 67% for new cases and new smear positive cases respectively. The provision of diagnosis and treatment according to the DOTS/Stop TB Strategy has resulted in major achievements in TB care and control. Between 1995 and 2011, 51 million people were successfully treated for TB in countries that had adopted the DOTS/Stop TB Strategy, saving 20 million lives. In countries reporting age-disaggregated data, most cases (88%) were aged 15–64 years. Children (aged <15 years) accounted for 6% of notified cases. The male: female ratio was 1.7 globally, ranging from 1.1 to 2.2 among WHO six regions. There are more than twenty drugs that are currently used for the treatment of TB and almost all of them were developed some years ago. The drugs are used in differing combinations in different circumstances, so that for example some TB drugs are only used for the treatment of new patients who are very unlikely to have resistance to any of the TB drugs. There are other drugs that are only used for the treatment of drug resistant TB.

The basic TB drugs (1st line drugs)

5 basic or 1st line TB drugs are;

Ethambutol is EMB or E,

Isoniazid is INH or H,

Pyrazinamide is PZA or Z,

Rifampicin is RMP or R,

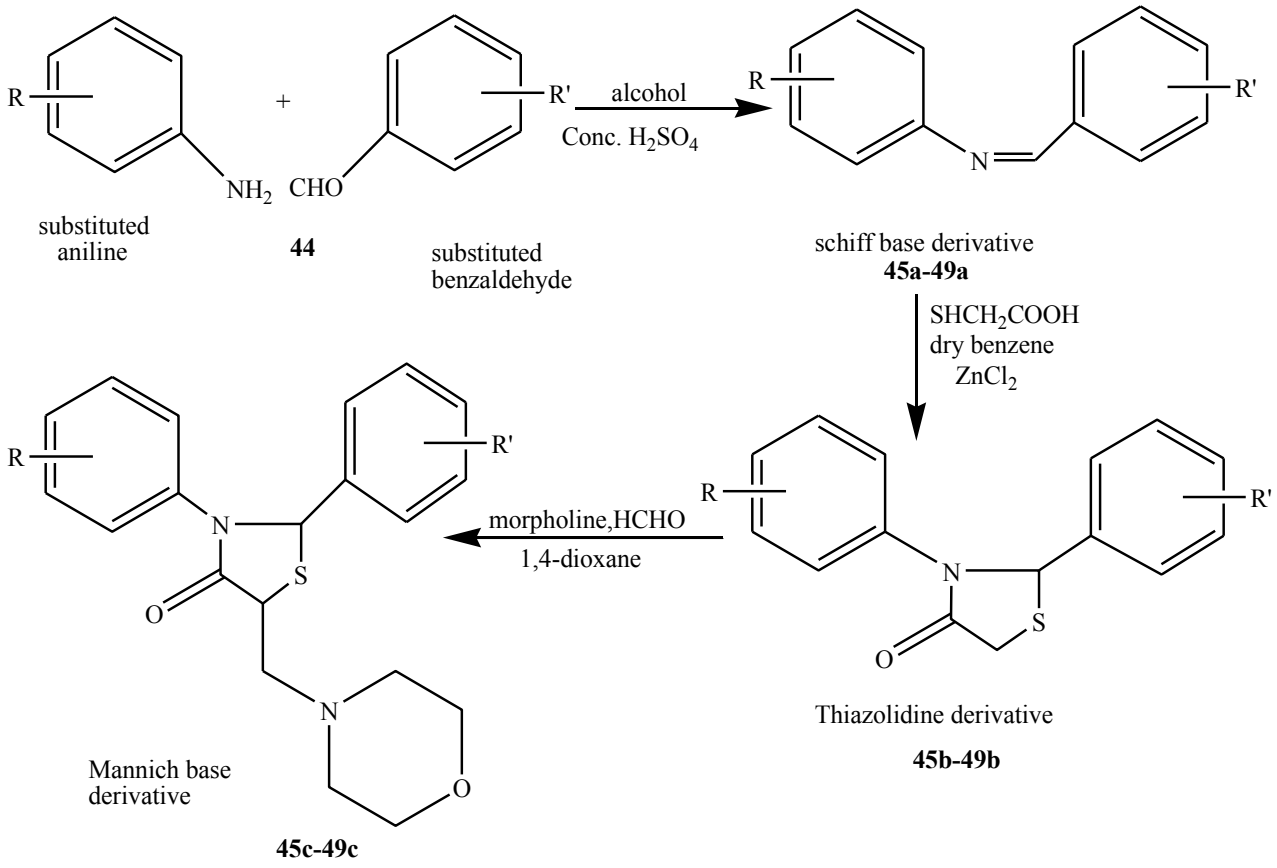
Streptomycin STM or S

All the other TB drugs are generally referred to as “second line” or reverse TB drugs. Classical drug discovery was solely based on observation of natural phenomena and consequences of relieved distress. Latest scientific technologies have helped to understand the drug action mechanism. Likewise the drug discovery procedures have changed. Computational chemistry and molecular modeling have become an essential part and an emerging tool for research and drug development process. The process of drug discovery is very complex and requires an interdisciplinary effort to design effective and commercially feasible drugs. The objective of

drug design is to find a chemical compound that can fit to a specific cavity on a protein target both geometrically and chemically.

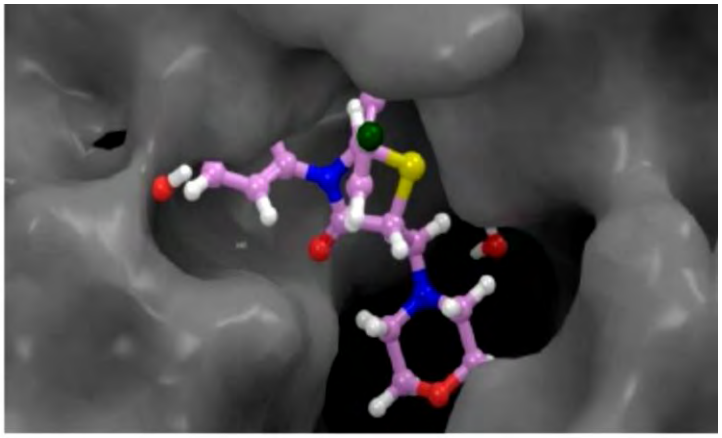
Molecular docking

Molecular docking is a computer simulation procedure to predict the conformation of a receptor-ligand complex, where the receptor is usually a protein or a nucleic acid molecule (DNA or RNA) and the ligand is either a small molecule or another protein. It can also be defined as a simulation process where a ligand position is estimated in a predicted or predefined binding site. The aim is to achieve an optimized conformation for both the protein and the ligand and relative orientation between them such that the free energy of the overall system is minimized. The two main stages of molecule docking are: a search stage that configures a certain number of possible binding of given protein and ligand and a scoring stage that estimates binding affinity for given protein, ligand, pose and conformations.



Substituent details in synthesized compounds

COMPOUND	R	R′
45a,45b,45c	4-Cl	4-Cl
46a,46b,46c	4-Cl	4-OCH_3
47a,47b,47c	4-Cl	3-NO_2
48a,48b,48c	4-Cl	2-Cl
49a,49b,49c	4-F	2-Cl



Docking image of Mycobacterium tuberculosis protein enoyl ACP reductase

Antitubercular activity

The synthesized analogue 45c, 46c and 47cwas selected for anti-tubercular activity. *Mycobacterium tuberculosis* H37Rv maintained in Lowenstein Jensen medium was used as the test organism for antimycobacterial screening studies. The bacterial cultures were grown till mid-log phase in the Middle brook 7H9 broth for *Mycobacterium tuberculosis* H37Rv. Stock solutions of the test compounds were prepared at a concentration of 2 mg/ml. 50 µL of the mid-log phase culture was added to 150µL of the media taken in microtitre plates. From the stock solution of the compounds 45c, 46c and 47c was added to the wells to final concentration of 100, 250, 500 µg/ml. The control wells contained culture without any compound. All the tests were done in duplicates. The plates were then incubated at 37°C for 7 days. After incubation 20µL of Resazurin dye was added and change of colour, if any was noted. The control wells showed no change of colour from pink. Those compounds which prevented the change of colour of the dye from blue to pink were considered to be inhibitory. It was found that all the selected mannich

base derivatives are active against *Mycobacterium tuberculosis* and from which 45c is more active than 46c and 47c. The MIC was defined as of the compounds were given below.

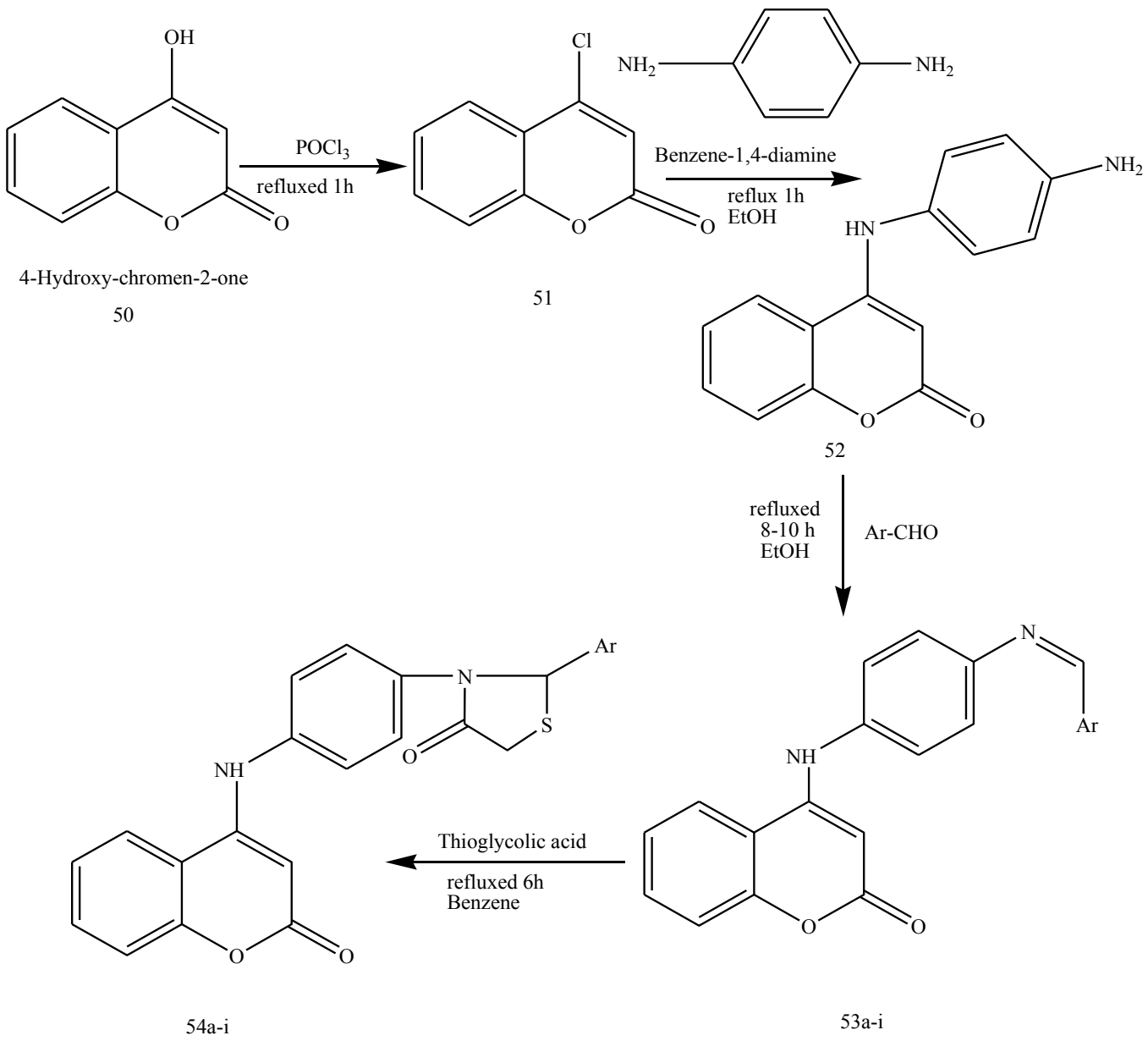
Table : MIC values (µg/ml) of 45c, 46c and 47c

Sl no:	Compound	MIC value (µg/ml)
1	45c	25
2	46c	50
3	47c	50

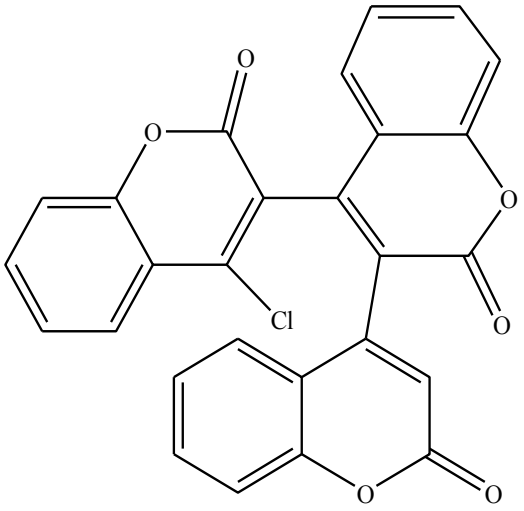
Compounds of Coumarin derivatives:

Coumarin and its derivatives represent one of the most active classes of compound possessing a wide spectrum of biological activity [243-245]. Novobiocin and chlorobiocin are established antimicrobials containing a coumarin skeleton [246]. In addition, these compounds are used as additives to food and cosmetics [247]. Coumarin derivatives are commonly used as optical whiteners, luminescence dyes [248], active media for lasers [249] and solar collector [250]. Various analogues of 4- substituted coumarin such as 4-chlorocoumarins exhibit antimicrobial activity. From the above line of reasoning we directed our work towards synthesis of various coumarin derivatives of biological interest using 4-chloro coumarin as a key starting material.

The aim of the present work was to synthesize new thiazolidinone derivatives containing coumarin moiety in order to find new biologically active compound. Thus, synthesis of novel 4-Thiazolidinones derivatives have been achieved.



Synthesis of thiazolidinone derivatives



55

4-Chloro-3, 4', 3', 4''-tercoumarin

Antimicrobial activity

All the synthesized compounds were tested for their antibacterial and antifungal activity (MIC minimum inhibition concentration) in vitro by broth dilution method with two gram positive bacteria *S. aureus* and *B. subtilis* and gram negative bacteria *E. coli*, *P. aeruginosa,* and fungi species like *C. albicans, A. niger* organisms taking ciprofloxacin, ampicillin, chloramphenicol, norfloxacin, flucanazole, griseofulvin, and Nystatin. Muller Hinton broth was used as nutrient medium to grow and dilute the drug suspension for test. DMSO was used as a diluent which not effected the growth of microbes. All the newly synthesized compounds were screened for their antimicrobial activity. From the result in table 18 Schiff base **53e** showed excellent activity when compared with ampicillin and chloramphenicol; while **54b, 54e, 54f** and **54i** demonstrated good activity against *E.coli* and **54e, 54i** significant activity against *P.aeruginosa*; while **53c, 54b, 54e, 54i** showed good activity against *S.aureus* and **54e** and **54i** demonstrated significant activity against *B.subtilis* when compared with standard drug ampicillin.

SOME NEW 1,3,4-THIADIAZOLE DERIVATIVES FOR THEIR ANTIMICROBIAL ACTIVITIES:

The structures of imidazo [2,1-b] [1,3,4]thiadiazoles are closely related to the biologically vibrant imidazo [1,3,4] thiazole heterocycles, in which the CH group in the thiazole ring is substituted by the isosteric nitrogen atom, but their properties often possess marked differences. The practically planar and rigid heteroaromatic imidazo [2, 1-b] [1,3,4] thiadiazole ring system

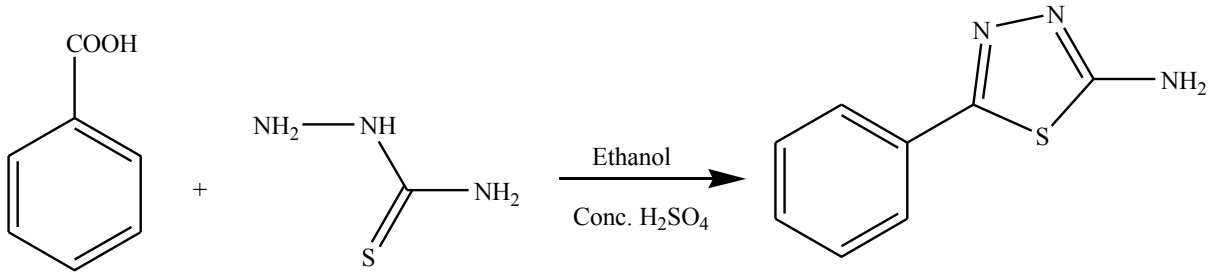
may therefore have interesting physicochemical and biological properties, because of the presence of four heteroatoms and two condensed heterocycles with different π-conjugation. Thiadiazole play a prominent role in nature. For example, the thiazolium ring present in vitamin B1 serves as an electron sink and its coenzyme form is important for thedecarboxylation of α-keto acids p [251]. Thiazoles were reported to possess antimicrobial [252], analgesic [253], anti inflammatory [254], anticancer [255], anti-tubercular [256], anthelmintic [257] & diuretic [258] activities. Thiazoles are easilymetabolized by routine biochemical reactions and are non-carcinogenic in nature [259]. In addition, pyrazoles are reported as anti-microbial [260], analgesic [261], anti inflammatory [262], anti hypertensive [263], anti-depressant [264] and anticancer [265] agents. Above observation prompted us to synthesize the title compounds **(60-66 and 69-72)** with presumption that drug intermediates based on thiosemicarbazide with various amines would produce novel thiadiazole derivatives with potent biological activities. Their chemical structure was confirmed by IR, ^{1}H NMR, and nitrogen estimation. These compounds were screened for their antibacterial activity against two gram $^{+}$ve bacteria (*Staphylococcus aureus* ATCC 9144, *Becillus Cereus* ATCC *11778* and two gram $^{-}$ve bacteria (*Escherichia coli* ATCC 25922*, Pseudomonas aeruginosa* ATCC 2853) and antifungal (*Aspergillus niger* ATCC 9029 and *Aspergillus fumigatus* ATCC 46645) activities by paper disc diffusion technique.

Antibacterial activity

All the newly synthesized 1, 3, 4-thiadiazole derivatives were screened for their antibacterial and antifungal activity. For antibacterial studies microorganisms employed were *Staphylococcus aureus* ATCC 9144*, Becillus Cereus* ATCC *11778, Escherichia coli ATCC 25922, Pseudomonas aeruginosa ATCC 2853*. For antifungal, *Aspergillus niger ATCC 9029 and Aspergillus fumigatus ATCC 46645* were used as organism. Both microbial studies were assessed by Minimum Inhibitory Concentration (MIC) by serial dilution method. For this, the compound whose MIC has to be determined is dissolved in serially diluted DMF Then a standard drop of the culture prepared for the assay is added to each of the dilutions, and incubated for 16–18 hrs at 37^{0}c. MIC is the highest dilution of the compound, which shows clear fluid with no development of turbidity.

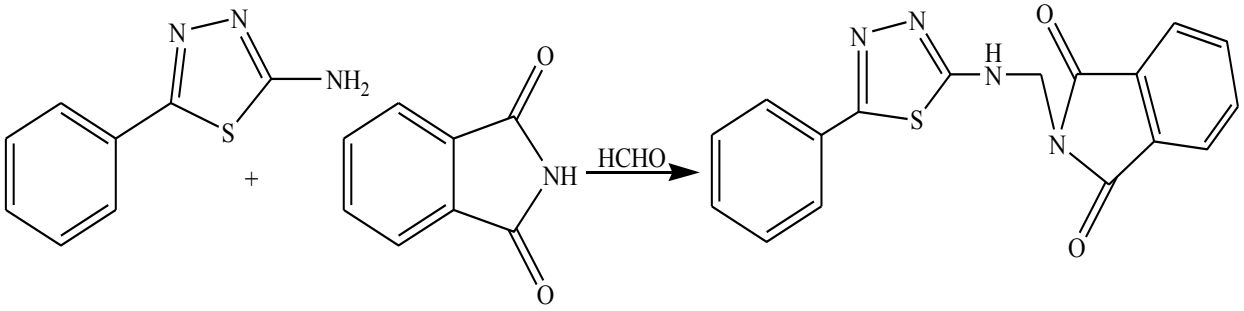
The structures of the synthesized compound were determined on the basis of their FTIR and ^{1}H NMR data. In vitro antibacterial activity data of 1, 3, 4-thiadiazole derivatives against tested

organisms displayed significant activity with a wide degree of variation. It is found that compound **60, 62 and 69** have shown significant antibacterial activity against gram positive bacteria. Rest of the compounds has exhibited significant to substantial activity against the same strain. Compound **62, 66** and **69** have shown highest activity against gram negative bacteria. Substantial activity is achieved in case of compounds **62** against *S. aureus, B. cereus, E. coli, P. aeruginosa* and the remaining compounds are significantly active against the same species. All the 1, 3, 4-Thiadiazole derivatives have exhibited significant to moderate activity against gram positive and gram negative bacteria. Derivatives **64** and **69** have exhibited substantial activity against *A. niger* and *C.* While derivatives **60, 66, 68** and **69** have shown higher activity against *A. fumigates.* Comparatively weak to moderate activity has been reported by remaining compounds. *E. coli* was found to be more susceptible than rest of the other strains of bacteria. From *in vitro* antifungal activity, data reveals that all the newly synthesized compounds displayed higher to week activity in comparison to standards. Thus, it is obvious from the structure-activity profile of substituted 1, 3, 4-Thiadiazole derivatives; a small structural variation may induce an effect on antibacterial activity.



Benzoic Acid **56** | Thiosemicarbazide **57** | 5-phenyl-1,3,4-thiadizol-2-amine **58**

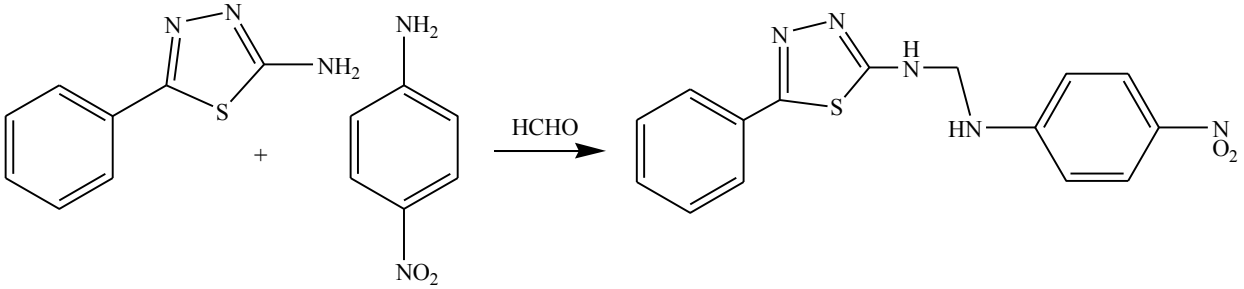
5-phenuyl-1, 3, 4-thiadiazole-2-amine



5-phenyl-1,3,4-thiadizol-2-amine Pthalamide

2-{[(5-phenyl-1,3,4-thiadiazol-2-yl)amino] methyl}-1H-isoindole-1,3(2H)-dione

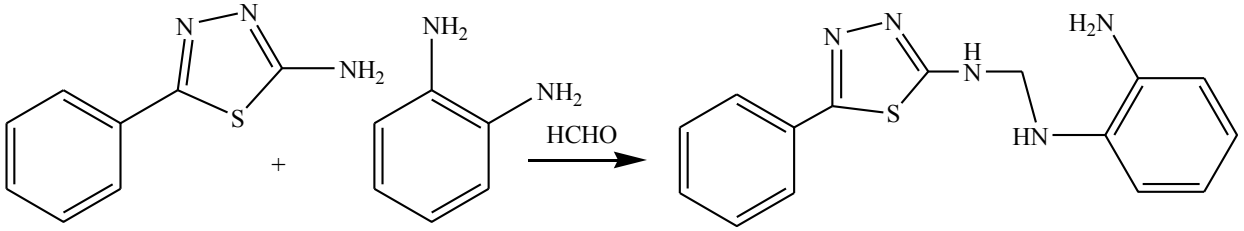
58 **59** **60**



5-phenyl-1,3,4-thiadizol-2-amine p-nitro aniline

N-(4-nitropheny l)-N'-(5-pheny l-1,3,4-thiadi azol-2-yl)methanediamine

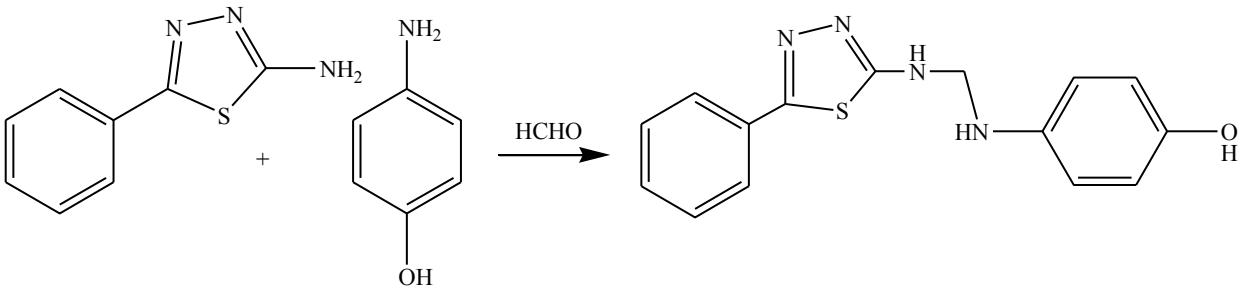
58 **61** **62**



5-phenyl-1,3,4-thiadizol-2-amine o-amino aniline

N-{[(5-phenyl-1,3,4-thiadiazol-2-yl)amino]methyl}benzene-1,2-diamine

58 **63** **64**

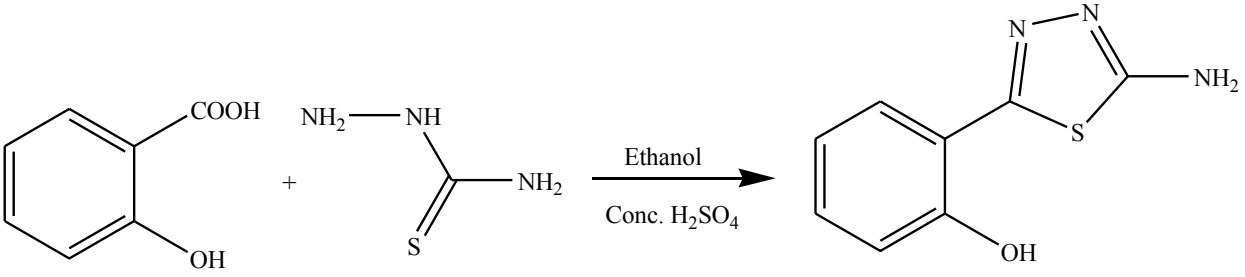


5-phenyl-1,3,4-thiadizol-2-amine
58

4-aminophenol
65

4-({[(5-phenyl-1,3,4-thiadiazol-2-yl)amino] methyl}amino)phenol
66

5-(substituted)-2-amino-thiadiazoles

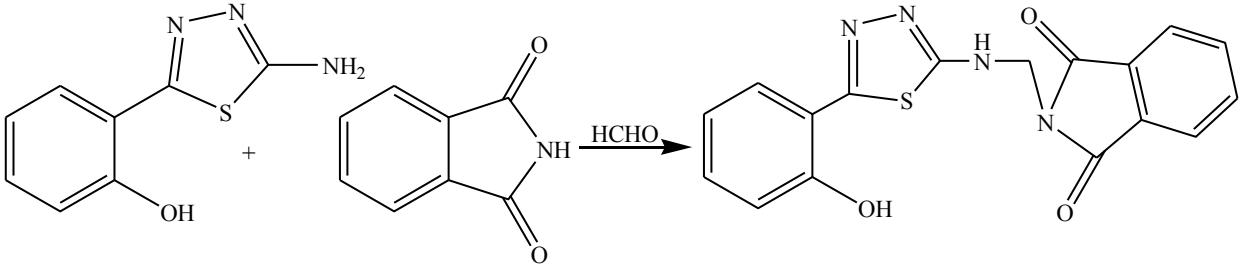


2-hydroxybenzoic acid
67

Thiosemicarbazide
57

2-(5-amino-1,3,4-thiadiazol-2-yl) phenol
68

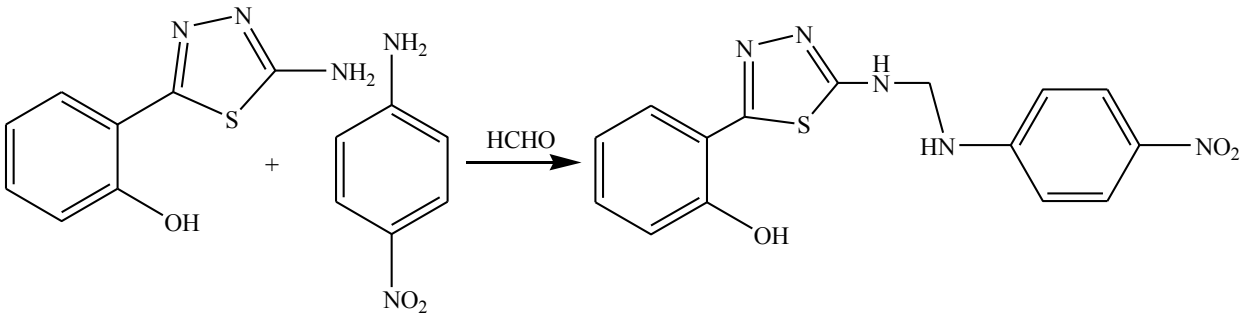
2-(5-amino-1, 3, 4-thiadiazol-2-yl)phenol



2-(5-amino-1,3,4-thiadiazol-2-yl)phenol
68

Pthalamide
59

2-({[5-(2-hydroxyphenyl)-1,3,4-thiadiazol-2-yl]amino}methyl)-1H-isoindole-1,3(2H)-dione
69



2-(5-amino-1,3,4-thiadia zol-2-yl)phenol

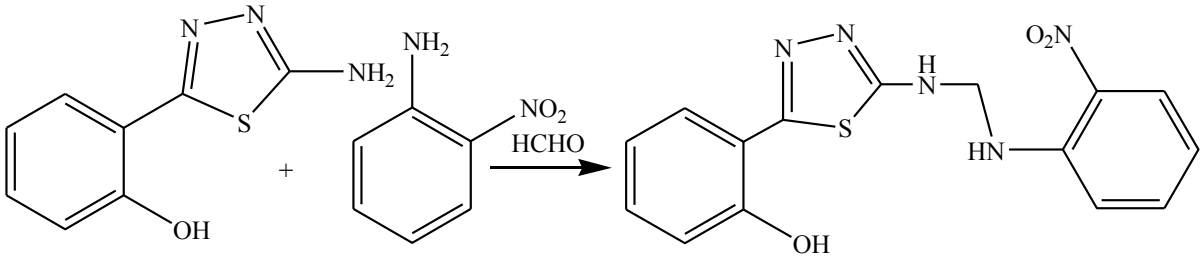
68

p-nitro aniline

61

2-[5-({[(4-nitrophenyl)amino]methyl} amino)-1,3,4-thiadiazol-2-yl]phenol

69



2-(5-amino-1,3,4-thiadia zol-2-yl)phenol

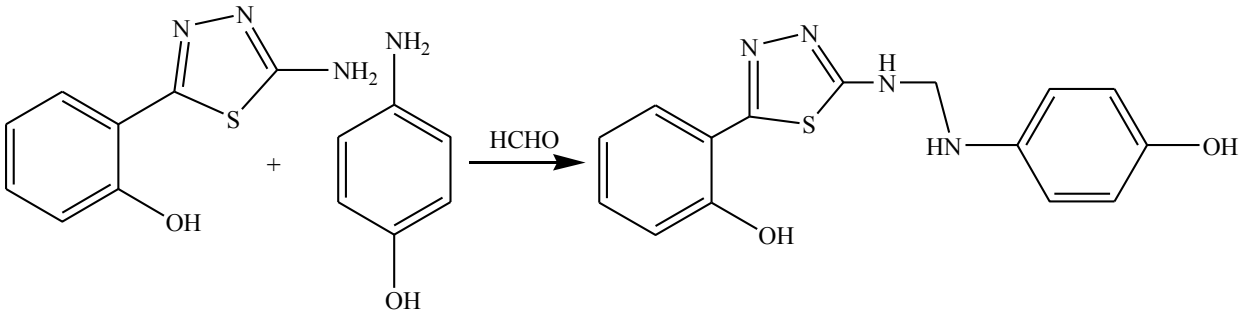
68

O-nitro aniline

70

2-[5-({[(2-nitrophenyl)amino]methyl} amino)-1,3,4-thiadiazol-2-yl]phenol

71



2-(5-amino-1,3,4-thiadia zol-2-yl)phenol

68

p-amino phenol

65

2-[5-({[(4-hydroxyphenyl)amino]methyl} amino)-1,3,4-thiadiazol-2-yl]phenol

72

5-(substituted)-2-amino-thiadiazole

IN VITRO ANTICANCER ACTIVITY OF NEW THIADIAZOLINES AND THIAZOLINONES CONTAINING A CHROMENYL SCAFFOLD

Malignant tumours represent one of the most serious threats against human health in the world, and the clinical prognosis remains relatively poor [266]. In 2008, cancer accounted for approximately eight million deaths worldwide [267] and the number of cases is expected to increase by more than 45% in the next 20 years [268]. Genotoxic agents have long targeted apoptotic cell death as a primary means of treating cancer [269, 270]. However, the presence of cellular defects in many cancers has contributed to an acquired resistance to apoptotic cell death [271, 272], thus lowering the effectiveness of chemo- and radiotherapies [269, 270]. Resistance to anoikis, a programmed cell death that occurs upon cell detachment from the extracellular matrix [273] is emerging as a hallmark of metastatic cancers that are resistant to conventional therapies [274]. Therefore, it is necessary to identify novel types of compounds that overcome the intrinsic resistance of cancer cells to pro-apoptotic stimuli by the induction of non-apoptotic cell death (such as autophagy or necrosis [269]) or by cytostatic effects [275]. For example, glioma is naturally resistant to pro-apoptotic stimuli [276] and therefore resistant to conventional therapies: the pro-autophagic alkylating agent temozolomide has significant therapeutic benefits for glioma patients [277, 278]. Similar observations can be made for melanoma [279, 280] and oesophageal cancers [281].

Molecules containing nitrogen- and sulphur-related heterocycles (thiazole, thiazolidine, thiazolinone, thiadiazoline) are considered important pharmacophores as they can possess interesting biological activities. For example, thiadiazolines have antihelmintic, antihypertensive, anticancer, anti-inflammatory, antibacterial, analgesic, and tyrosinase inhibitory activities [282].

Thiazolinones display hypoglycaemic, antibacterial, antifungal, anti-tuberculous, anti-HIV and also antitumoural activities [283]. Chromones are a group of naturally occurring compounds that are ubiquitous, especially in plants [284, 285]. In addition to forming the basic nucleus of an entire class of natural products, the flavones, the chromone moiety forms an important component of the pharmacophores found in many molecules with medicinal significance: tyrosine and protein kinase C inhibitors, antifungal, antiallergenic, antiviral, antitubulin, antihypertensive, and anticancer agents. Consequently, considerable attention is being devoted to the isolation of these compounds from natural resources and partial versus complete syntheses of

chromone derivatives as well as to the evaluation of their biologic activity [284, 285]. Herein we report the synthesis and *in vitro* growth inhibition characterization of new thiadiazoline and thiazolinone derivatives substituted with a chromen-3-yl or 3 chromenylmethylene moiety. We screened six human cancer cell lines with various levels of resistance to pro-apoptotic stimuli to investigate whether the compounds in the study are able to overcome this resistance. Three cell lines display various levels of resistance to pro-apoptotic stimuli, i.e., the A549 non-small-cell-lung cancer (NSCLC) [286, 287], the SKMEL-28 melanoma [288] and the U373 glioma [289, 290] cell lines. Two of the cell lines display actual sensitivity to pro-apoptotic stimuli, i.e., the Hs683 glioma [290, 291] and the MCF-7 breast carcinoma [292] cell lines. The *in vitro* anti-proliferative activity of each compound in the study has been determined using the MTT colorimetric assay [288-291]. The three most potent compounds were further analyzed using computer-assisted phase-contrast microscopy, i.e. quantitative video microscopy [293, 294].

Chemistry

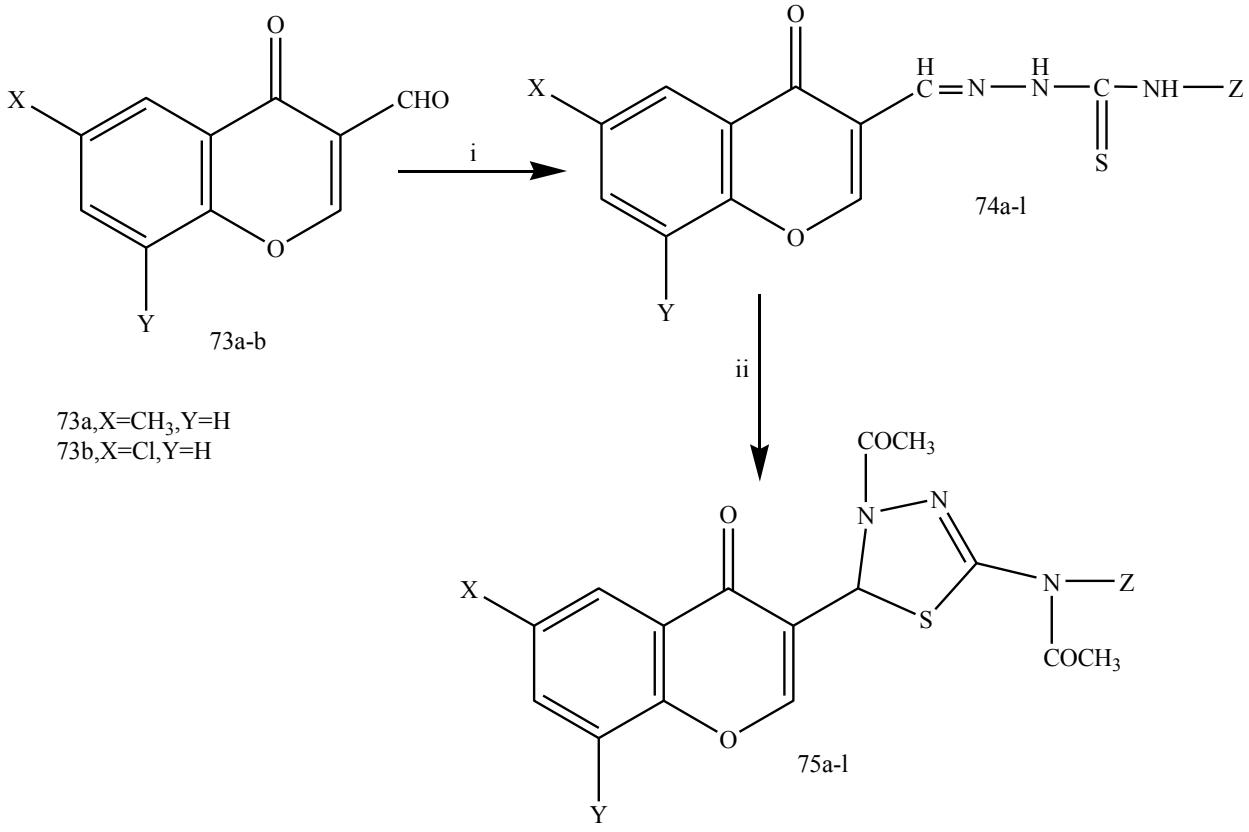
Solvents were obtained from commercial sources. Analytical thin layer chromatography was carried out on precoated Silica Gel $60F_{254}$ sheets using UV absorption for visualisation. The melting points were taken with Electrothermal and MPM-H1 Schorpp melting point meters and are uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were recorded at room temperature on a Bruker Avance NMR spectrometer operating at 500 MHz and were in accordance with the assigned structures. Chemical shift values were reported relative to tetramethylsilane (TMS) as the internal standard. The samples were prepared by dissolving the powder of the synthesized compounds in DMSO-d_6 (δ_H= 2.51 ppm) and the spectra were recorded using a single excitation pulse of 12 μs (^{1}H NMR). GC-MS analyses were performed with an Agilent gas chromatograph 6890 equipped with an apolar Macherey Nagel Permabond SE 52 capillary column. Elemental analysis was measured with a Vario El CHNS instrument. *Determination of In Vitro Growth Inhibition Activity in Human Cancer Cells*. Seven human cancer cell lines were obtained from the American Type Culture Collection (ATCC, Manassas, USA), the European Collection of Cell Culture (ECACC, Salisbury, UK) and the *Deutsche Sammlung von Mikroorganismen und Zellkulturen* (DSMZ, Braunschweig, Germany). These seven cell lines included the A549 non-small-cell lung cancer (NSCLC; DSMZ code ACC107), the SKMEL-28 melanoma (ATCC code HTB-72), the Hs683 oligodendroglioma (ATCC code HTB-138), the U373 (ECACC code 08061901), the T98G (ATCC; code CRL-1690) and U251 (ECACC code 09063001)

glioblastoma and the MCF-7 breast cancer (DSMZ; code ACC115) cell lines. The cells were cultured in RPMI (Lonza, Verviers, Belgium) culture medium supplemented with 10% heat-inactivated foetal calf serum (Lonza), 4 mM glutamine, 100 μg/ml gentamicin and penicillin-streptomycin (200 U/ml and 200 μg/ml; Lonza).The overall growth level of each cell line was determined using the colorimetric MTT (3- [4,5-dimethylthiazol-2yl-diphenyl tetrazolium bromide, Sigma, Belgium) assay as detailed previously [288-291]. The data are represented as the mean values from one experiment with six replicates in each experimental condition. *Computer-Assisted Phase-Contrast Microscopy (Video-microscopy).* The direct visualization of the compound-induced effects on the cell proliferation and morphology was carried out by means of computer-assisted phase contrast microscopy, i.e. quantitative video-microscopy, as detailed elsewhere [293, 294].

Chemistry

Our synthetic routes to the target compounds **75a-l**, **78** are shown in Schemes 12-13, the synthesis of compound **70** being reported previously [295]. The structure of compound **6** is presented in. The derivatives of chromenyl-4, 5-dihydrothiadiazoles **75a-l** were prepared by reacting the obtained chromenyl-thiosemicarbazones **74a-l** with the cyclisation agent acetic anhydride in the presence of small quantities of pyridine as a catalyst [292, 296, 297]. The intermediate thiosemicarbazones **74a-l** were obtained by a simple condensation between the 3-formyl-chromones **75a,b** and *N*4-substituted thiosemicarbazides in absolute ethanol using concentrated sulphuric acid as catalyst [298,299]. The *N*4-substituted phenyl, methyl, allyl, 3-trifluoro-methyl-phenyl, and 4- methoxy-phenyl thiosemicarbazides were obtained in good yields (>90%) by the addition of hydrazine hydrate to phenylisothiocyanate, methylisothiocyanate, allylisothiocyanate, 3-trifluoromethylphenyl- isothiocyanate and 4-methoxyphenyl-isothiocyanate, respectively, with stirring in absolute ethanol at room temperature for 3 h (3000). These thiosemicarbazides are also commercially available. The 5-chromenyl-methylene-2-thioxo-4-thiazolidinone 77 was obtained by the condensation of 2-thioxo-4-thiazolidinone with the 3-formyl-chromone **76** in glacial acetic acid at reflux and in the presence of anhydrous sodium acetate. After isolation and purification, the obtained derivative **77** was alkylated with 2-iodoacetamide in the presence of anhydrous potassium hydroxide in dimethylformamide at room temperature to obtain the novel *N*-substituted compound **78**.

The purity of the compounds was confirmed by TLC, and all new compounds were characterized by m. p., elemental analysis and spectroscopic data (^{1}H NMR, ^{13}C NMR, MS).



73a-b

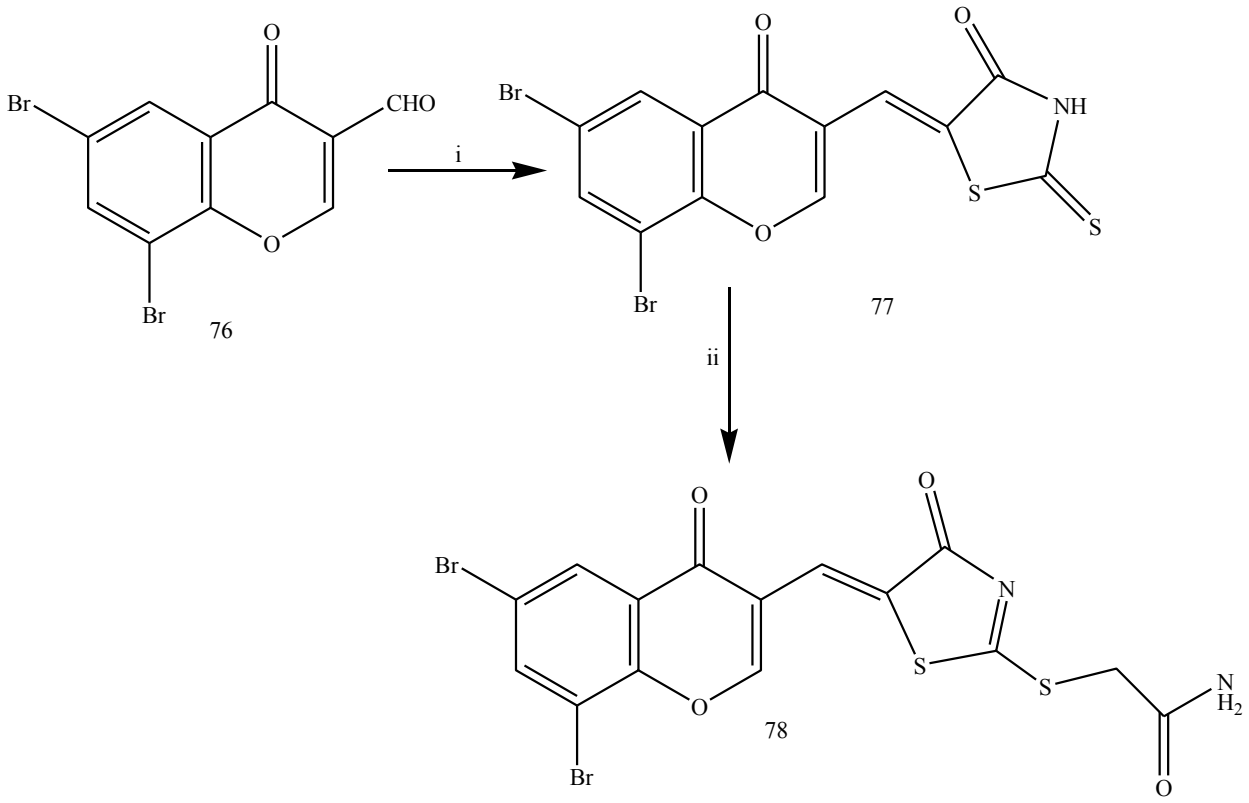
73a,X=CH_3,Y=H
73b,X=Cl,Y=H

74a-l

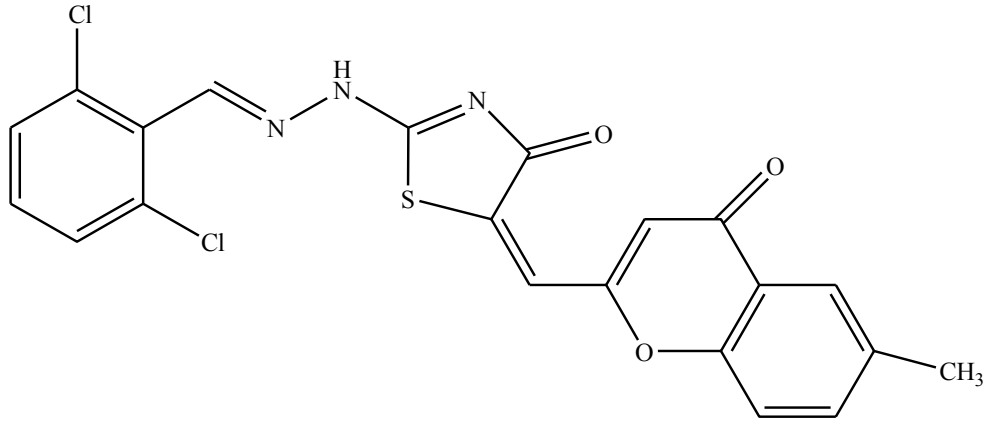
75a-l

75a, X=CH_3, Y=H, Z=CH_3
75b, X=CH_3, Y=H, Z=C_6H_5
75c, X=CH_3, Y=H, Z=$CH_2CH{=}CH_2$
75d, X=Cl, Y=H, Z=CH_3
75e, X=Cl, Y=H, Z=C_6H_5
75f, X=Cl, Y=H, Z=$CH_2CH{=}CH_2$
75g, X=CH_3, Y=H, Z=C_6H_4 -4 -OCH_3
75h, X=CH_3, Y=H, Z=C_6H_4 -3 -CF_3
75i, X=CH_3, Y=H, Z=H
75j, X=Cl, Y=H, Z=H
75k, X=Cl, Y=H, Z=C_6H_4 -4 -OCH_3
75l, X=Cl, Y=H, Z=C_6H_4 -3 -CF_3

chromen-yl-thiadiazoline derivatives 78a-l: (i) $H_2NNHCSNHZ$/abs EtOH, reflux 3 h; (ii) Ac_2O/pyridine, reflux 4 h



chromen-yl-methylene-thiazolin-2-thioacetamide ; (i) Thiazolidine-2-thioxo-4-one/AcOH, AcONa, reflux 3 h; (ii) ICH_2CONH_2/KOH, DMF, rt, 3 h



Chemical structure of compound 79

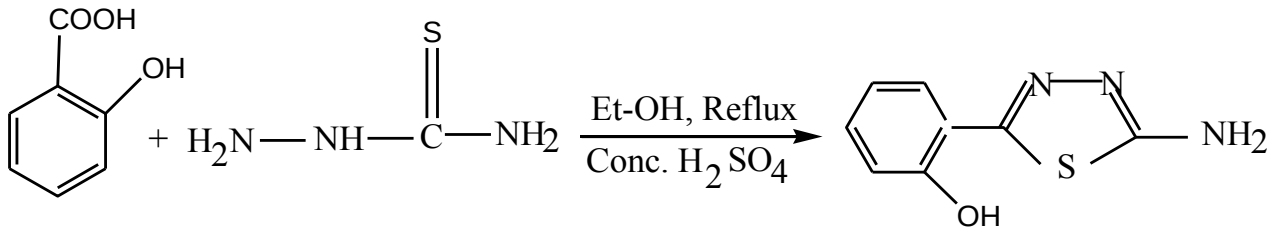
Characterization of in vitro anticancer activity

The data in Table 1 show that the most potent compounds displayed an *in vitro* IC50 ranging between 12 (**78h**) and 35 (**78l**, **78k**, **78j**) μM, while the remaining compounds in the study displayed weak or no (> 100 μM for **78i**) *in vitro* growth inhibition activity. In fact, nine of the

14 compounds in the study displayed an anti proliferative activity of < 100 μM against all cancer cell lines that were analyzed. Compound **67h** displayed the highest *in vitro* anticancer activity. Structure Activity Relationship (SAR) analyses indicate that, of the two chemical series that were investigated, the chromenyl-thiadiazolines displayed the highest *in vitro* anticancer activity. With respect to the thiadiazoline derivatives (**78a-l** compounds), the substitution of the exocyclic amine with a substituted-phenyl moiety increased the *in vitro* growth inhibition of cancer cells, 3-trifluoromethyl-phenyl-derivatives (**78h**, **78 l**) displaying the highest growth inhibition activity. Thiazolinones **78** and **79** showed moderate growth inhibition activity against the cancer cell lines that were analyzed in the current study. So, it seems that the presence of fluorine atoms induces positive influences on the anti-proliferative activity of these compounds against cancer cells. The data in Table 22 further reveal that the most potent compounds, i.e., **78h**, **78j**, **78k** and **78 l**, display similar growth inhibition effects in cancer cells independently of whether these cells are associated (A549 [287, 288], SKMEL-28 [289], U373 [290, 291]) or not associated (Hs683 [291, 292], MCF-7 [293]) to various levels of resistance to pro-apoptotic stimuli. Compounds **78h**, **78k** and **78l** were further assayed by means of quantitative video microscopy. Compounds **78h** and **78l** induced morphological cytostatic effects in the human MCF-7 breast cancer and T98G glioblastoma (data not shown) cell lines, while the compound **78k** induced morphological cytotoxic effects in both the human MCF-7 breast cancer and the T98G glioblastoma (data not shown) cell lines. In fact, these three compounds induced cell death rates that ranged between 15 and 30% in both human MCF-7 breast cancer and T98G glioblastoma cells. Therefore, the quantitative determination of cell death did not enable a clear distinction to be made between 78h- and 78l-related cytostatic effects versus effects from 78k. But that information was obtained via morphological analyses. Indeed, the panels on the right in shows that 78h- and 78l-related cytostatic effects parallel a delay in MCF-7 (and also T98G. data not shown) cell growth .while 78k-induced cytotoxic effects are paralleled by complete growth inhibition I MCF-7 breast cancer and in T98G glioblastoma (data not shown) cells.

Chapter 2
Experimental

2.1 Synthesis of 5(*o*-hydroxyphenyl)-2-amino-1, 3, 4-thiadiazole



1 **2** **3**

A mixture of thiosemicarbazide (0.01 mol, 0.91gm), salicylic acid (0.01mol, 1.38 gm) and concentrated sulfuric acid (1.2 ml) in 10.8 ml of ethanol was taken in a round bottomed flux. The reaction mixture was then stirred for one hour and 50 minutes under reflux condition. The progress of the reaction was monitored by TLC. The reaction mixture was then poured into crushed ice and the crude product was separated by filtration. The crude was then recrystallized from ethanol. An off-white solid with 82% yield was obtained and the melting point was recorded as (145-150 ^{o}C).

IR (KBr, cm^{-1}, Fig. **1**) : 3380-3440 (O-H, phenolic), 3280-3360 (N-H, amine), 3120 (C-H, aromatic), 1640 (C=N), 1553, 1480, 1440 (C=C, aromatic), 889 (C-S-C).

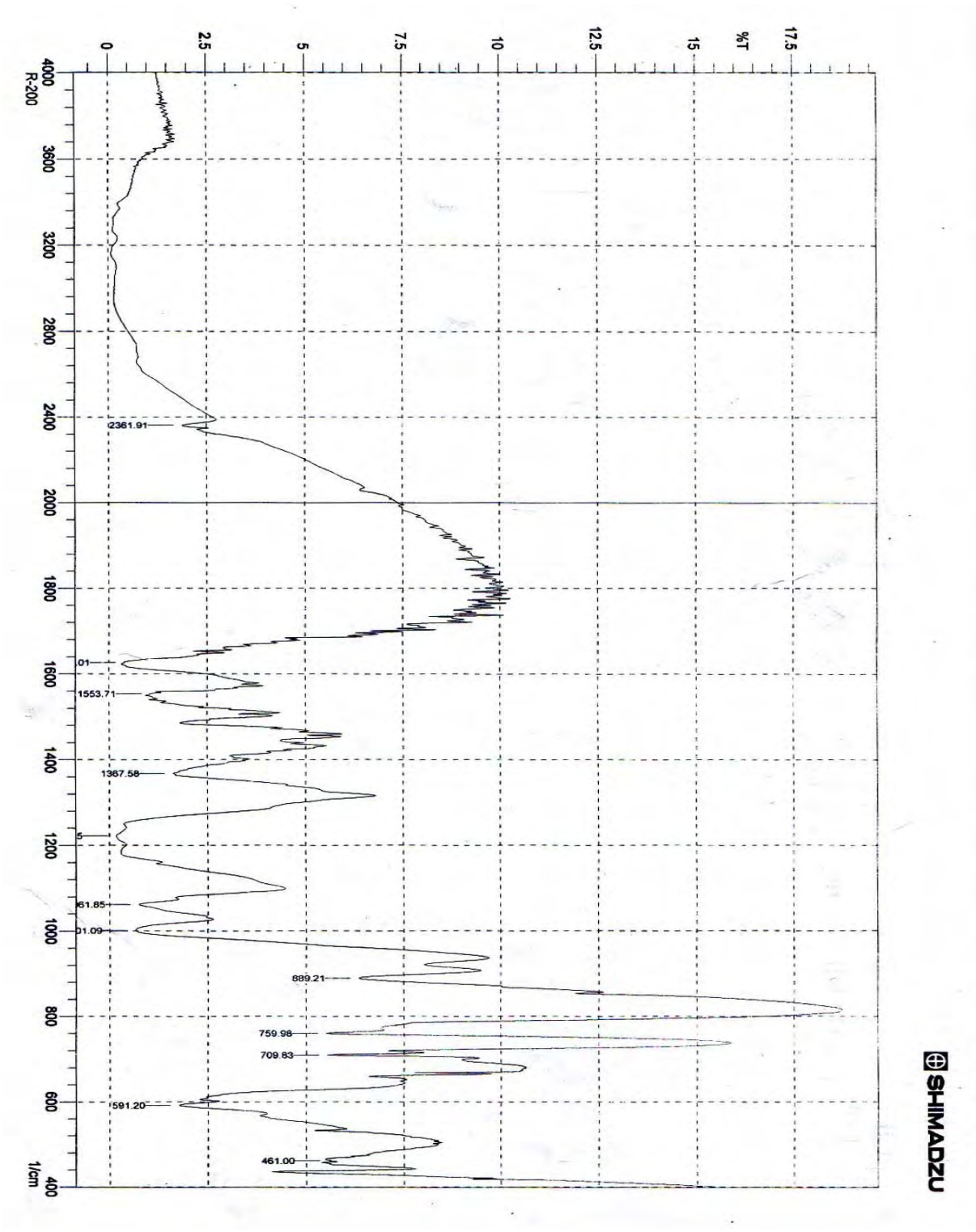
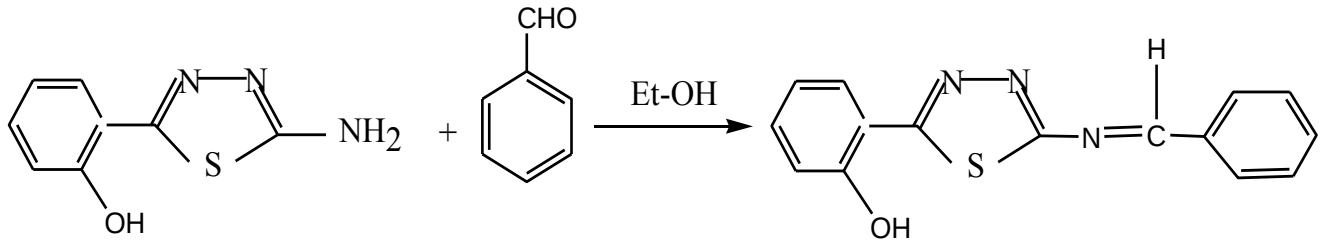


Figure 1: IR spectrum of 5(*o*-hydroxyphenyl)-2-amino-1, 3, 4-thiadiazole

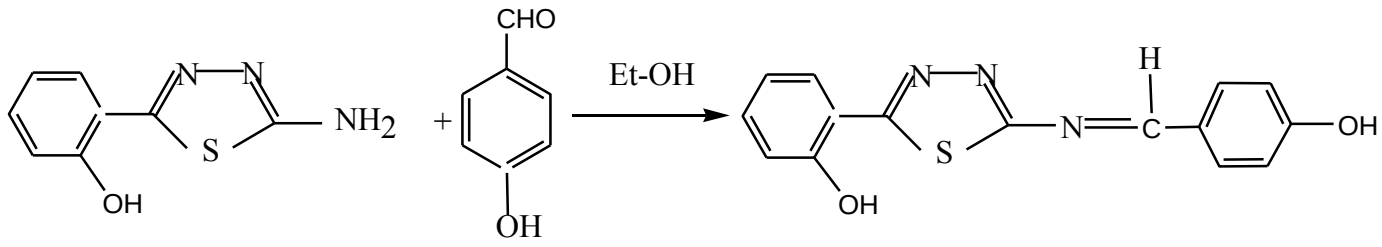
2.2 Synthesis of 5(*o*-hydroxyphenyl)-2(benzylideneamino) -1, 3, 4-thiadiazole



3 **4** **5**

A solution of **3** (0.002072 mol, 0.4 gm) and benzaldehyde (0.002072 mol, 0.219689 gm) in ethanol was taken in a round bottomed flux and the mixture was refluxed for two hours in water bath. The progress of the reaction was monitored by TLC. The reaction mixture was then poured into ice water. A light yellow coloured precipitate was separated by filtration. The crude light yellow product was then used for the next step reaction.

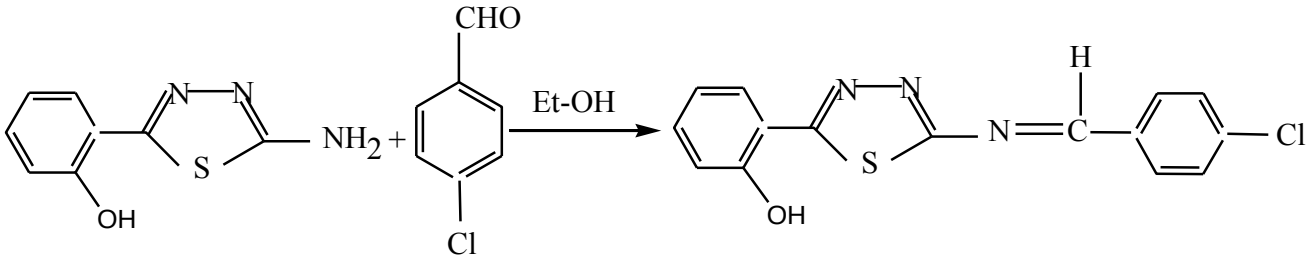
2.3 Synthesis of 5(*o*-hydroxyphenyl)-2(*p*-hydroxybenzylideneamino) -1, 3, 4-thiadiazole



3 **6** **7**

A solution of **3** (0.0020725 mol, 0.4 gm) and 4-hydroxybenzaldehyde (0.0020725 mol, 0.252849 gm) in ethanol was taken in a round bottomed flux and the mixture was refluxed for one and half hour. The progress of the reaction was monitored by TLC. The reaction mixture was poured into ice water. A light yellow precipitate was separated by filtration. The crude light yellow product was then used for the production of thiazolidinone.

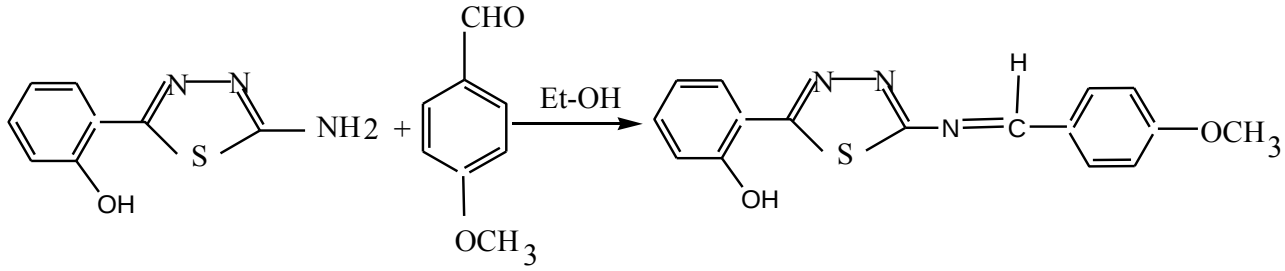
2.4 Synthesis of 5(*o*-hydroxyphenyl)-2(*p*-chlorobenzylideneamino) -1, 3, 4-thiadiazole



3 **8** **9**

A solution of **3** (0.001554404 mol, 0.3 gm) and 4-cholorobenzaldehyde (0.001554404 mol, 0.21839376 gm) in ethanol was taken in a round bottomed flux and the mixture was stirred for two and half hours at reflux condition. The progress of the reaction was monitored by TLC. The reaction mixture was then poured into ice water. A white color precipitate was separated by filtration. The crude white product was then used for the next step reaction.

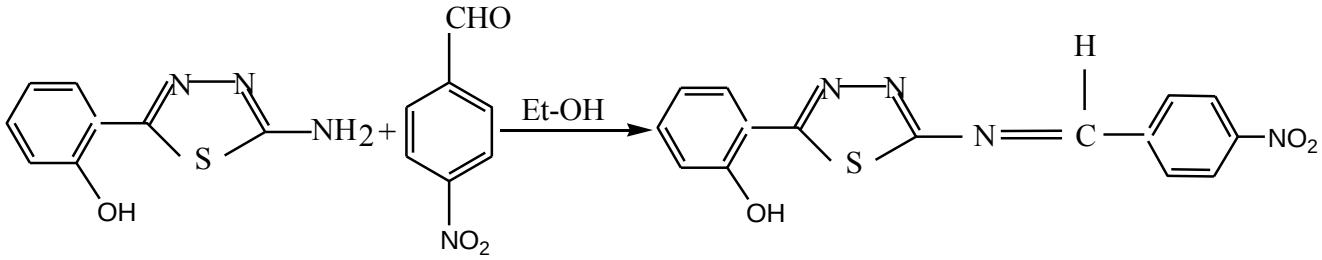
2.5 Synthesis of 5(*o*-hydroxyphenyl)-2(*p*-methoxybenzylideneamino) -1, 3, 4-thiadiazole



3 **10** **11**

A solution of **3** (0.002590674 mol, 0.5 gm) and 4-methoxybenzaldehyde (0.002590674 mol, 0.352331 gm) in ethanol was taken in a round bottomed flux and the mixture was stirred for one hour and 40 minutes under reflux condition. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into ice water. The solid crude product was separated by filtration and dried in a desiccator. The crude was then used for the production of thiazolidinone.

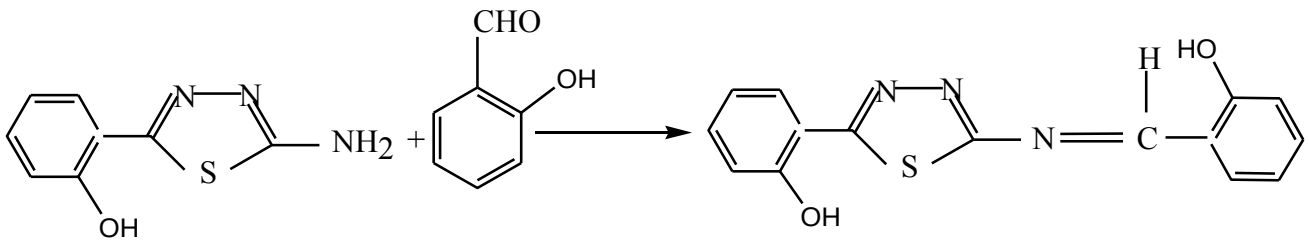
2.6 Synthesis of 5(*o*- hydroxyphenyl)-2(*p*-nitrobenzylideneamino) -1, 3, 4-thiadiazole



3 **12** **13**

A solution of **3** (0.003367876 mol, 0.65 gm) and *p*-nitrobenzaldehyde (0.003367876 mol, 0.50854928 gm) in ethanol was taken in a round bottomed flux and the mixture was stirred for one hour at reflux condition. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into ice water. The solid crude product was separated by filtration and dried in a desiccator. The crude was then used for the next step reaction.

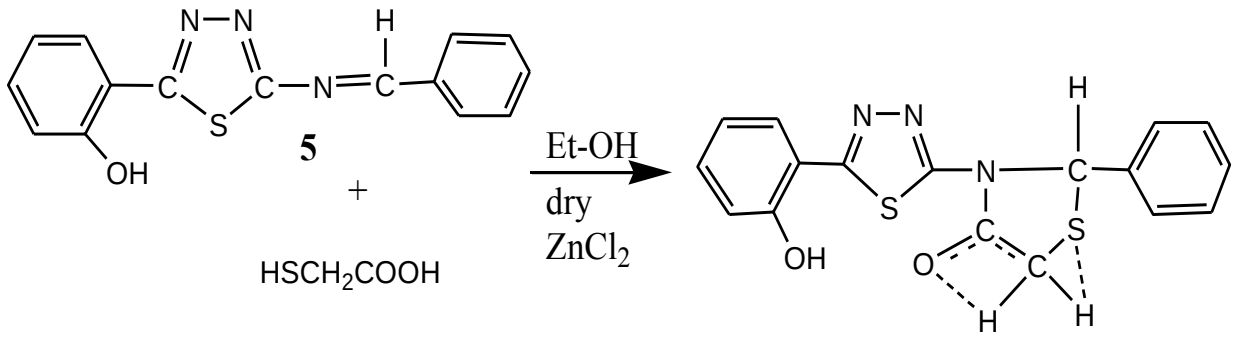
2.7 Synthesis of 5(*o*- hydroxyphenyl)-2(*o*-hydroxybenzylideneamino) -1, 3, 4-thiadiazole



3 **14** **15**

A solution of **3** (0.001554404 mol, 0.3 gm) and salicylaldehyde (0.001554404 mol, 0.189637 gm) in ethanol was taken in a round bottomed flux and the mixture was stirred for three hours under reflux condition. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into ice water. The solid crude product was separated by filtration and dried in a desiccator. The crude was then used for the production of thiazolidinone.

2.8 Synthesis of 3(5′- *o*-hydroxyphenyl -1′, 3′, 4′-thiadiazolyl)-2(phenyl)-thiazolidin-4-one



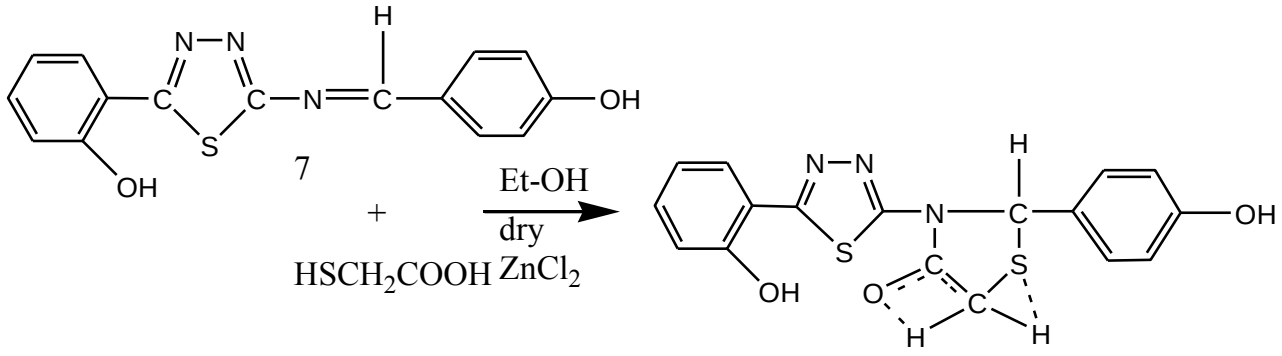
16 **17**

A solution of **5** (0.001067 mol, 0.3 gm) and mercapto acetic acid (0.001067 mol, 0.098220 gm) in ethanol was taken in a round bottomed flask. A pinch amount of dry zinc chloride was added in this mixture as a catalyst. Then the reaction mixture was stirred under reflux condition for ten hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was poured into ice water and the white solid crude material was separated by filtration. The crude product was then purified by recrystallization from ethanol and white crystalline product with 67% yield was isolated and the melting point was recorded as (178-185) ^{0}C.

IR (KBr, cm^{-1}, Fig. **2**): 3430 (O-H, phenolic), 3256 (O-H, H-bonded), 3157 (C-H, aromatic), 2983 (C-H, aliphatic), 1648 (C=O), 1598 (C=N), 1544, 1480, 1447 (C=C, aromatic), 816 (C-S-C).

^{1}H NMR (400 MHz, DMSO-d$_6$, Fig **3-4**): δ 7.398-7.411 (m, 5H, aromatic), 7.788-7.810 (m, 4H, aromatic), 7.991 (bd, s, 1H, CO-CH-S), 8.054 (s, 1H, -N-CH-Ph), 8.200 (bd, s, 1H, -CO-CH-S), 11.430 (s, 1H, phenolic-OH).

2.9 Synthesis of 3(5′- *o*-hydroxyphenyl -1′, 3′, 4′-thiadiazolyl)-2(*p*-hydroxyphenyl)-thiazolidin-4-one



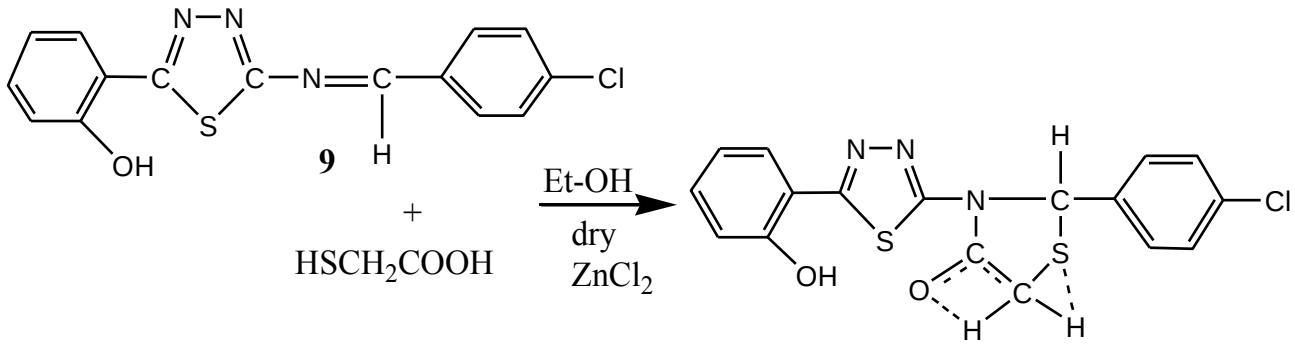
A solution of **7** (0.0006734 mol, 0.2 gm) and mercapto acetic acid (0.0006734 mol, 0.061952 gm) in ethanol was taken in a round bottomed flask. A pinch amount of dry zinc chloride was added in this mixture as a catalyst. Then the reaction mixture was stirred under reflux condition for ten hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was poured into ice water and the cream solid crude material was separated by filtration. The crude product was then purified by recrystallization from ethanol and cream crystalline product with 62% yield was isolated and the melting point was recorded as (239-241) ^{0}C.

IR (KBr, cm^{-1}, Fig. **5**): 3440-3520 (O-H, phenolic), 3360-3390 (O-H, phenolic), 3256 (O-H, H-bonded), 3120 (C-H, aromatic), 2980 (C-H, aliphatic), 1648 (C=O), 1586 (C=N), 1547, 1511, 1445 (C=C, aromatic), 821 (C-S-C).

^{1}H NMR (400 MHz, DMSO-d$_6$, Fig **6-7**) : δ 6.771 (bd, s, 2H, Ar-H), 6.793 (bd, s, 2H, Ar-H), 7.602 (bd, s, 2H, Ar-H), 7.623 (bd, s, 2H, Ar-H), 7.823 (bd, s, 1H, -CO-CH-S), 7.956 (s, 1H, N-CH-Ph), 8.053 (bd, s, 1H, -CO-CH-S), 9.884 (bd, s, 1H, -PhOH), 11.243 (s, 1H, Ph-O-H).

^{13}C NMR (100 MHz, DMSO-d$_6$, Fig. **8**) : δ 115.77 (Ar-C), 116.53 (Ar-C), 117.16 (Ar-C), 119.56 (Ar-C), 119.81 (Ar-C), 120.13 (Ar-C), 120.71 (Ar-C), 125.36 (Ar-C), 127.27 (Ar-C), 128.33 (Ar-C), 129.51 (Ar-C), 131.63 (Ar-C), 140.63 (CO-CH$_2$-S), 154.41 (C=N), 156.86 (C=N), 169.97 (N-CH-Ph), 178.13 (C=O).

2.10 Synthesis of 3(5′-*o*-hydroxyphenyl-1′,3′,4′-thiadiazolyl)-2(*p*-chlorophenyl)-thiazolidin-4-one



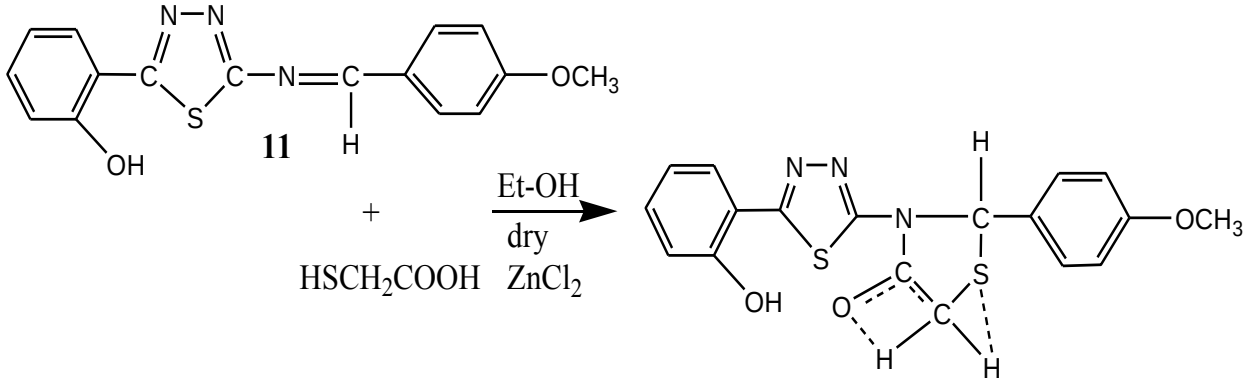
16 **19**

A solution of **9** (0.0009033281 mol, 0.285 gm) and mercapto acetic acid (0.0009033281 mol, 0.083106 gm) in ethanol was taken in a round bottomed flask. A pinch amount of dry zinc chloride was added in this mixture as a catalyst. Then the reaction mixture was stirred under reflux condition for thirteen hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was poured into ice water and the off white solid crude material was separated by filtration. The crude product was then purified by recrystallized from ethanol and off white crystalline product with 78% yield was isolated and the melting point was recorded as (206-209) ^{0}C.

IR (KBr, cm^{-1}, Fig. **9**): 3440 (O-H, phenolic), 3280 (O-H, H-bonded), 3156 (C-H, aromatic), 2980 (C-H, aliphatic), 1650 (C=O), 1600 (C=N), 1520, 1491, 1460 (C=C), 815 (C-S-C).

^{1}H NMR (400 MHz, DMSO-d_6, Fig. **10**) : δ 7.435-7.442 (bd, s, 2H, Ar-H), 7.45-7.463 (bd, s, 2H, Ar-H), 7.802-7.806 (bd, s, 2H, Ar-H), 7.823 (w, s, 2H, Ar-H), 8.023 (w, s, 1H, CO-CH_2-S,1H, N-CH-Ph), 8.174 (bd, s, 1H, CO-CH_2-S), 11.437 (s, 1H, O-H).

2.11 Synthesis of 3(5′- *o*-hydroxyphenyl -1′, 3′, 4′-thiadiazolyl)-2(*p*-methoxyphenyl)-thiazolidin-4-one

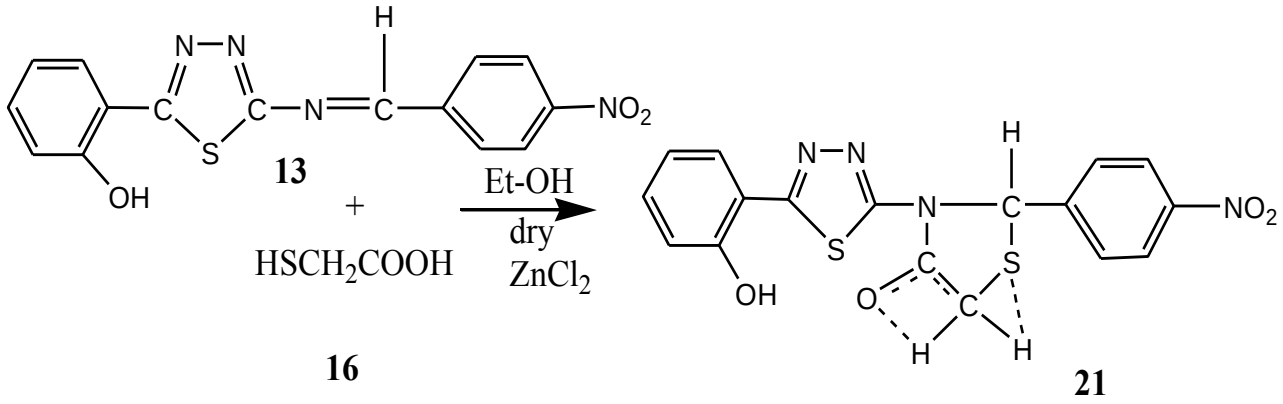


A solution of **11** (0.0007717 mol, 0.24 gm) and mercapto acetic acid (0.0007717 mol, 0.070996 gm) in ethanol was taken in a round bottomed flask. A pinch amount of dry zinc chloride was added in this mixture as a catalyst. Then the reaction mixture was stirred under reflux condition for eleven hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was poured into ice water and the white solid crude material was separated by filtration. The crude product was then purified by recrystallization from ethanol and white crystalline product with 76% yield was isolated and the melting point was recorded as (179-181) ^{0}C.

IR (KBr, cm^{-1}, Fig. **11**): 3400 (O-H, phenolic), 3290 (O-H, H-bonded), 3153 (C-H, aromatic), 2990 (C-H, aliphatic), 1640 (C=O), 1600 (C=N), 1537, 1520, 1440 (C=C), 835 (C-S-C).

^{1}H NMR (400 MHz, DMSO-d_6, Fig. **12**) : δ 3.788 (s, 3H, OCH_3), 6.944 (bd, s, 2H, Ar-H), 6.966 (bd, s, 2H, Ar-H), 7.720 (bd, s, 2H, Ar-H), 7.741 (bd, s, 2H, Ar-H), 7.903 (w, 1H, CO-CH-S), 7.990 (s, 1H, N-CH-Ph), 8.099 (w, s, 1H, CO-CH-S), 11.306 (s, 1H, O-H).

2.12 Synthesis of 3(5′- *o*-hydroxyphenyl -1′, 3′, 4′-thiadiazolyl)-2(*p*-nitrophenyl)-thiazolidin-4-one

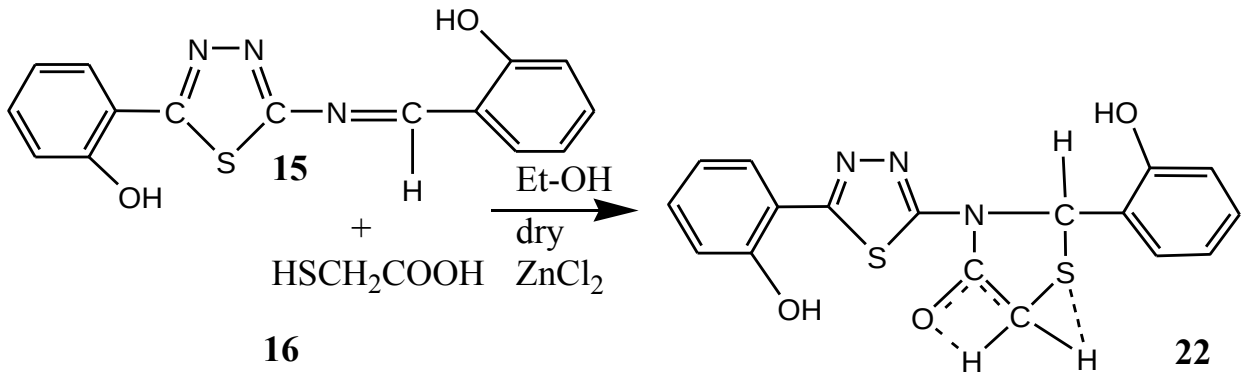


A solution of **13** (0.0009202454 mol, 0.3 gm) and mercapto acetic acid (0.0009202454 mol, 0.084662 gm) in ethanol was taken in a round bottomed flask. A pinch amount of dry zinc chloride was added in this mixture as a catalyst. Then the reaction mixture was stirred under reflux condition for seven hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was poured into ice water and the yellow solid crude material was separated by filtration. The crude product was then purified by recrystallization from ethanol and yellow crystalline product with 64% yield was isolated and the melting point was recorded as $(243\text{-}245)^0$C.

IR (KBr, cm^{-1}, Fig. **13**): 3480 (O-H, phenolic), 3367 (O-H, H-bonded), 3148 (C-H, aromatic), 2996 (C-H, aliphatic), 1650 (C=O, weak), 1580 (C=N), 1577, 1516, 1453 (C=C), 1340 (N=O), 820 (C-S-C).

^{1}H NMR (400 MHz, DMSO-d_6, Fig. **14**) : δ 8.090 (bd, s, 2H, Ar-H), 8.112 (bd, s, 2H, Ar-H), 8.131 (bd, s, 2H, Ar-H), 8.219 (bd, s, 2H, Ar-H), 8.241 (s, 1H, N-CH-Ph), 8.262 (w, s, 1H, CO-CH-S), 8.404 (w, s, 1H, CO-CH-S), 11.171 (s, 1H, -O-H).

2.13 Synthesis of 3(5′- *o*-hydroxyphenyl -1′, 3′, 4′-thiadiazolyl)-2(*o*-hydroxyphenyl)-thiazolidin-4-one



A solution of **15** (0.0006734 mol, 0.2 gm) and mercapto acetic acid (0.0006734 mol, 0.061952 gm) in ethanol was taken in a round bottomed flask. A pinch amount of dry zinc chloride was added in this mixture as a catalyst. Then the reaction mixture was stirred under reflux condition for twelve hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was poured into ice water and the reddish yellow or coffee colored solid crude material was separated by filtration. The crude product was then purified by recrystallization from ethanol and the reddish yellow crystalline product with 69% yield was isolated and the melting point was recorded as (216-219) ^{0}C.

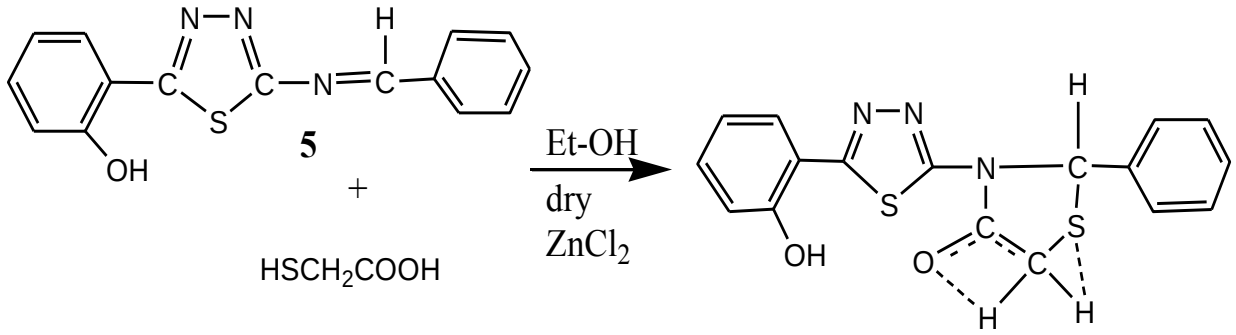
IR (KBr, cm^{-1}, Fig. **15**): 3445 (O-H, phenolic), 3320 (O-H), 3147 (C-H, aromatic), 2936 (C-H, aliphatic), 1640 (C=O), 1600 (C=N), 1500, 1490, 1446 (C=C), 830 (C-S-C).

^{1}H NMR (400 MHz, DMSO-d$_6$, Fig. **16**) : δ 6.802-6.875 (m, 5H, Ar-H), 7.196-7.238 (m, 4H, Ar-H), 7.882-7.899 (w, 1H, CO-CH-S), 8.053 (w, 1H, CO-CH-S), 8.372 (s, 1H, N-CH-Ph), 9.960 (s, 1H, O-H), 11.358 (s, 1H, O-H).

Chapter 3
Results and Discussion

3.1 Characterization of 3(5′- *o*-hydroxyphenyl -1′, 3′, 4′-thiadiazolyl)-2(phenyl)-thiazolidin-4-one

The compound **17** was synthesized by refluxing equimolar mixture of 5(*o*-hydroxyphenyl)-2(benzylideneamino) -1, 3, 4-thiadiazole and mercapto acetic acid in ethanol in presence of catalytic amount of zinc chloride. The progress of the reaction was monitored by TLC. After work up a white crystalline product with 67% yield was obtained and the melting point was recorded as (178-185) ^{0}C.

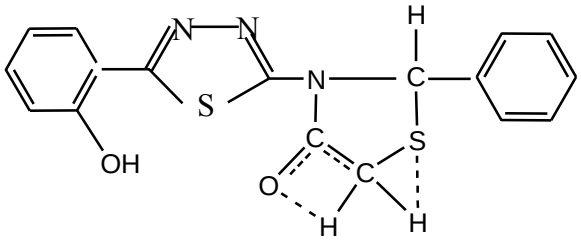


16 **17**

The IR spectrum (Fig. **2**) showed a peak at 3430 cm^{-1} was assigned for phenolic O-H. The weak broad band at 3256 cm^{-1} was distinctive for hydrogen bonded O-H. The peak at 3157 cm^{-1} was identified for aromatic C-H stretching. The aliphatic C-H stretching was observed at 2983 cm^{-1}. The weak absorption band at 1648 cm^{-1} was designated for enolic C=O group. The endocyclic C=N peak was attributed 1598 cm^{-1}. The characteristic bands at 1544 cm^{-1}, 1480 cm^{-1}, 1447 cm^{-1} were ascribed for aromatic C=C. The C-S-C linkage was designated at 816 cm^{-1}.

The ^{1}H NMR spectrum (Fig. **3-4**) showed a multiplet at 7.398-7.411was assigned for five aromatic protons. Another multiplet was designated for four aromatic protons at 7.888-7.810. The singlet at 7.991 was designated for deshielded hydrogen bonded one proton of nearby carbonyl group. The sharp singlet for one benzylic proton was identified at 8.054. The broad singlet of one hydrogen bonded proton of nearby carbonyl group was distinctive at 8.200. The down fielded phenolic proton was designated at 11.430.

All the above spectral evidences witnessed in favor of the structure of the compound **17** as



17

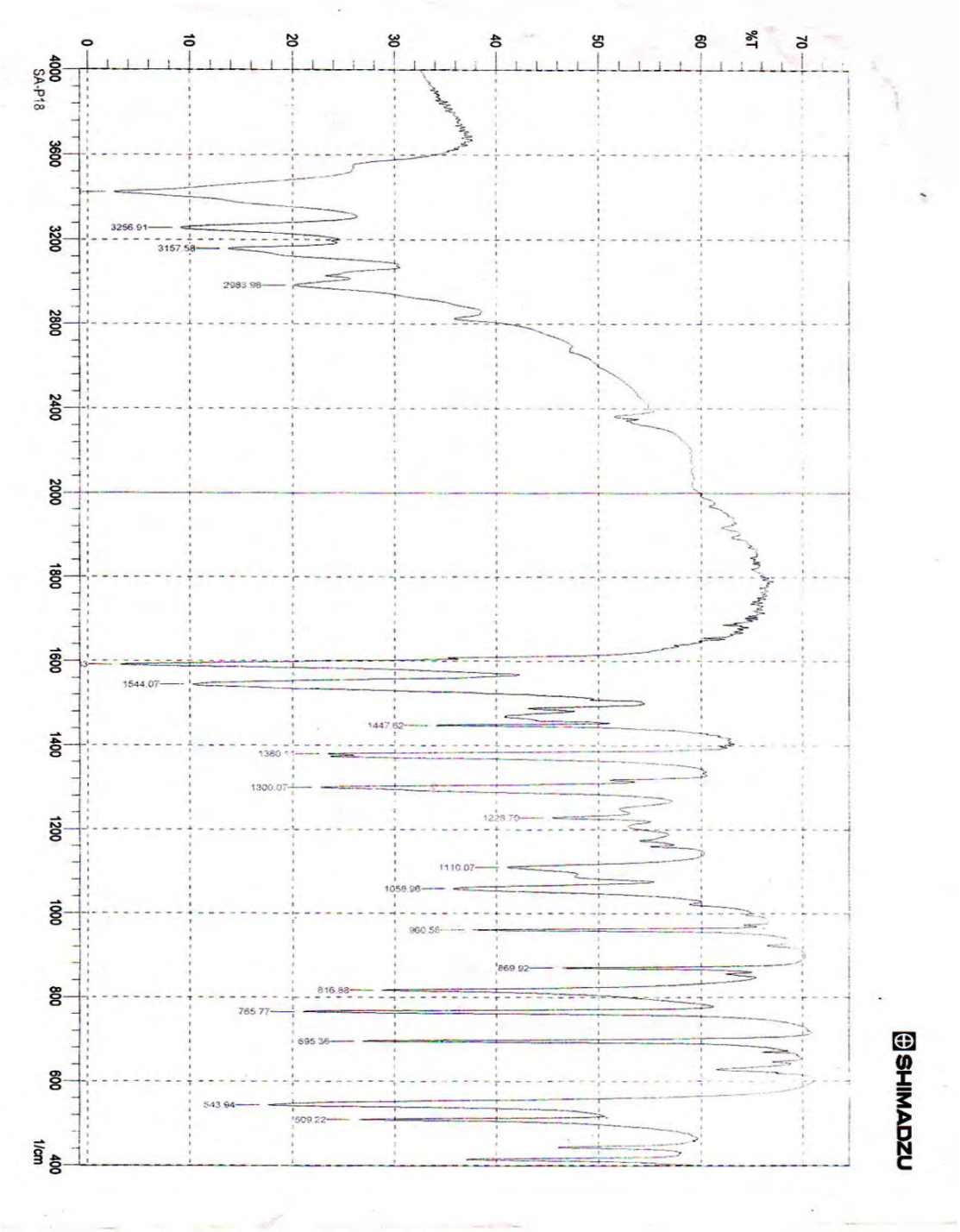


Figure 2: IR spectrum of compound 3(5′- *o*-hydroxyphenyl - 1′, 3′, 4′-thiadiazolyl)-2(phenyl)-thiazolidin-4-one

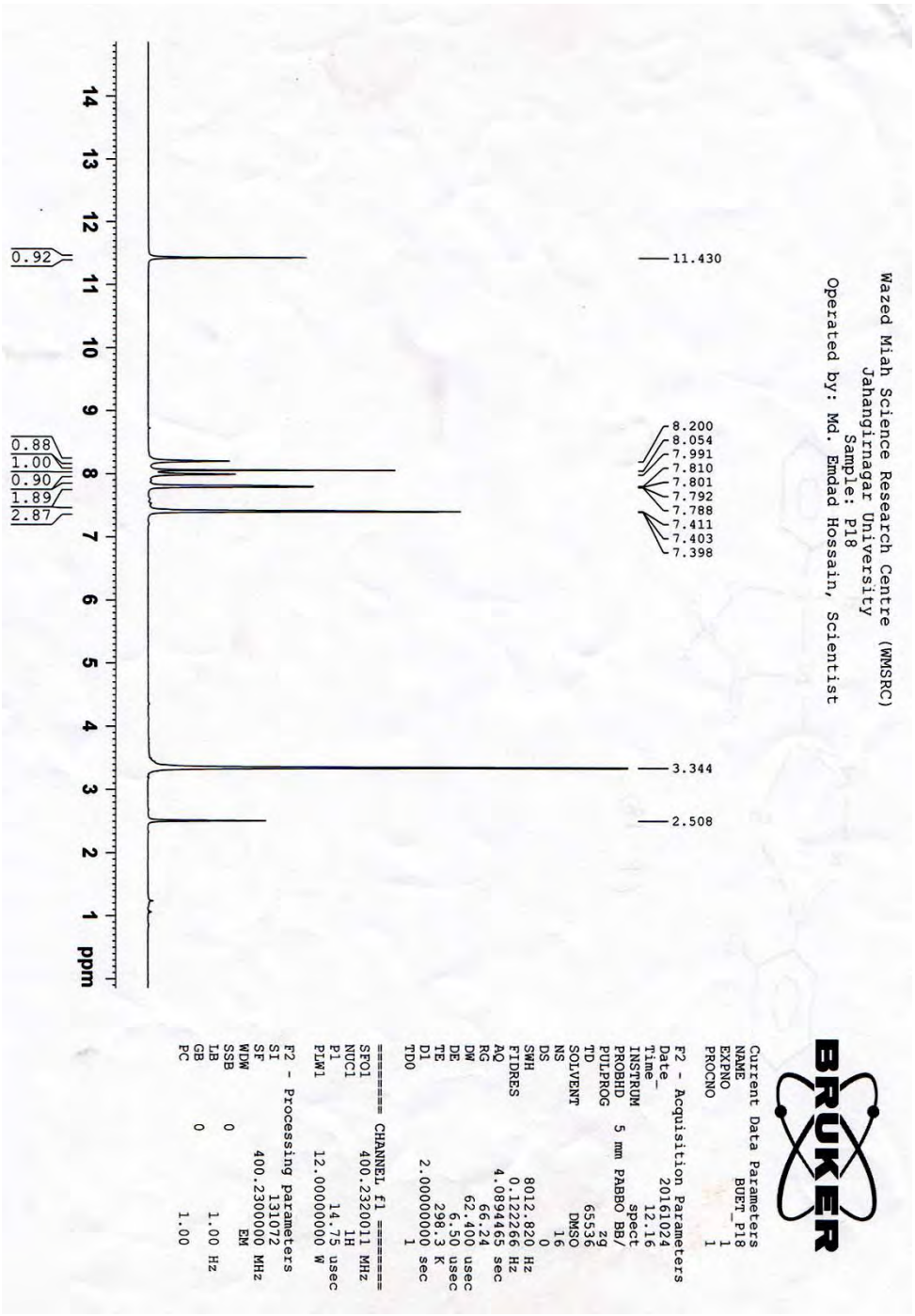


Figure 3: ^{1}H NMR of compound 3(5′- *o*-hydroxyphenyl - 1′, 3′, 4′-thiadiazolyl)-2(phenyl)-thiazolidin-4-one

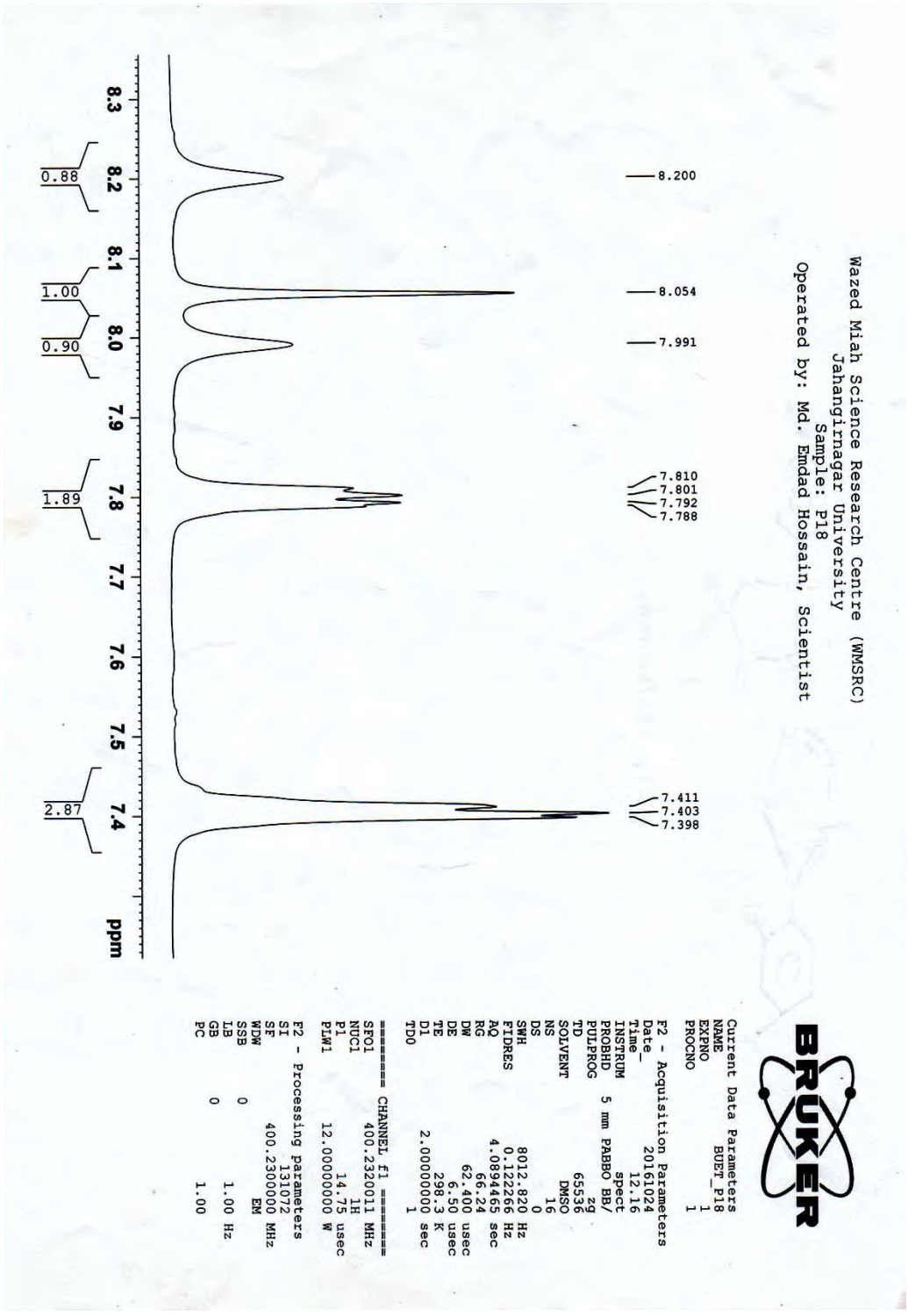
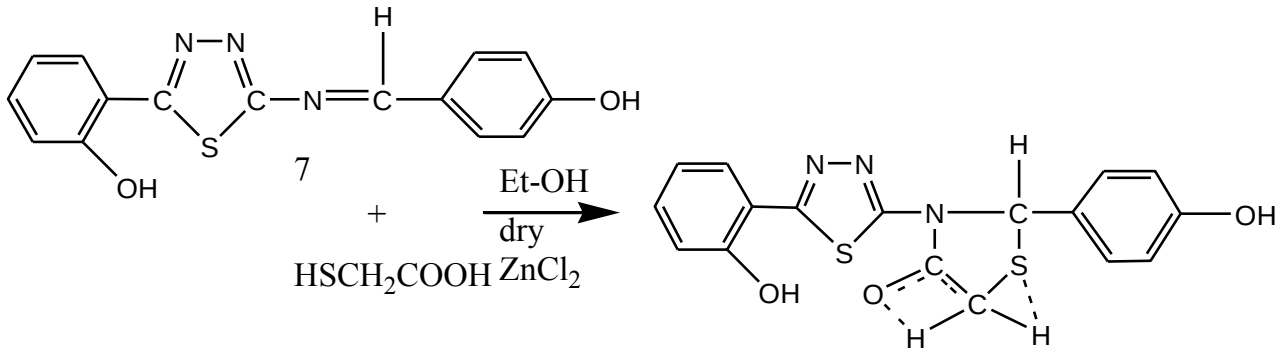


Figure 4: ^{1}H NMR (extention) of compound 3(5′- *o*-hydroxyphenyl -1′, 3′, 4′-thiadiazolyl)-2(phenyl)-thiazolidin-4-one

3.2 Characterization of 3(5′- *o*-hydroxyphenyl -1′, 3′, 4′-thiadiazolyl)-2(*p*-hydroxyphenyl)-thiazolidin-4-one

The compound **18** was synthesized by refluxing equimolar mixture of 5(*o*-hydroxyphenyl)-2(*p*-hydroxybenzylideneamino) -1, 3, 4-thiadiazole and mercapto acetic acid in ethanol in presence of catalytic amount of zinc chloride. The progress of the reaction was followed by TLC. After work up, a cream crystalline product with 62% yield was obtained and the melting point was recorded as (239-241) ^{0}C.



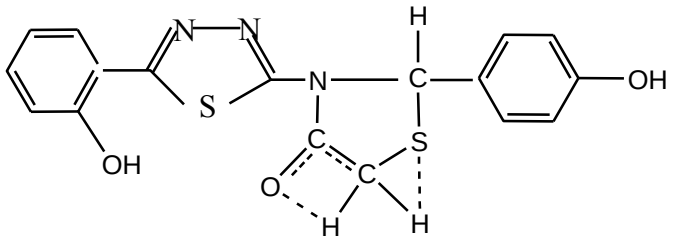
The IR spectrum (Fig. **5**) of the compound **18** showed a weak band at 3440-3520 cm^{-1} was assignable for the phenolic O-H group. Another contemporary weak band at 3360-3390 cm^{-1} was detective for the phenolic O-H group. The peak at 3256 cm^{-1} was suggestive for the enolic O-H group of hydrogen bonded C=O group. The characteristics aromatic and aliphatic C-H stretching were observed at 3120 cm^{-1} and 2980 cm^{-1} respectively. The C=O absorption peak was designated in the longer wavelength at 1648 cm^{-1} due to the keto-enol tautomerism for hydrogen bonding. The intensified peak at 1586 cm^{-1} was attributed for C=N group. The characteristic peaks at 1547, 1511 and 1445 cm^{-1} were identified for aromatic C=C. The C-S-C linkage was ascribed at 821 cm^{-1}.

The ^{1}H NMR spectrum (Fig. **6-7**) of the compound **18** showed a broad singlet for two aromatic protons at 6.77. Another contemporary broad singlet for two aromatic protons was detected at

6.793. Similarly the two other broad singlet of equal intensity for four identical aromatic protons were designated at 7.602 and at 7.623 respectively. The sharp singlet at 7.823 was distinctive for one proton of -CO-CH-S-. The benzylic deshielded singlet proton was detected at 7.956. The broad singlet at 8.053 was identified for one proton of -CO-CH-S-. The broad singlet at 9.884 was attributed for one proton of phenolic O-H. The other phenolic O-H proton was detectable at 11.243.

The ^{13}C NMR spectrum (Fig. **8**) showed the signals at 115.77, 116.53, 117.00, 119.56, 119.81, 120.13, 120.71, 125.36, 127.27, 128.33, 129.51 and 131.63 were assignable for aromatic carbons. The signal at 140.63 was indicative for 1C of $–CH_2$-, 1C of C=N at 154.41, 1C of another C=N at 156.86, one benzylic carbon at 169.97 and the down fielded signal at 178.13 was distinctive for 1C of C=O.

All the above spectral evidences express harmony with the structure of the compound **18** as



18

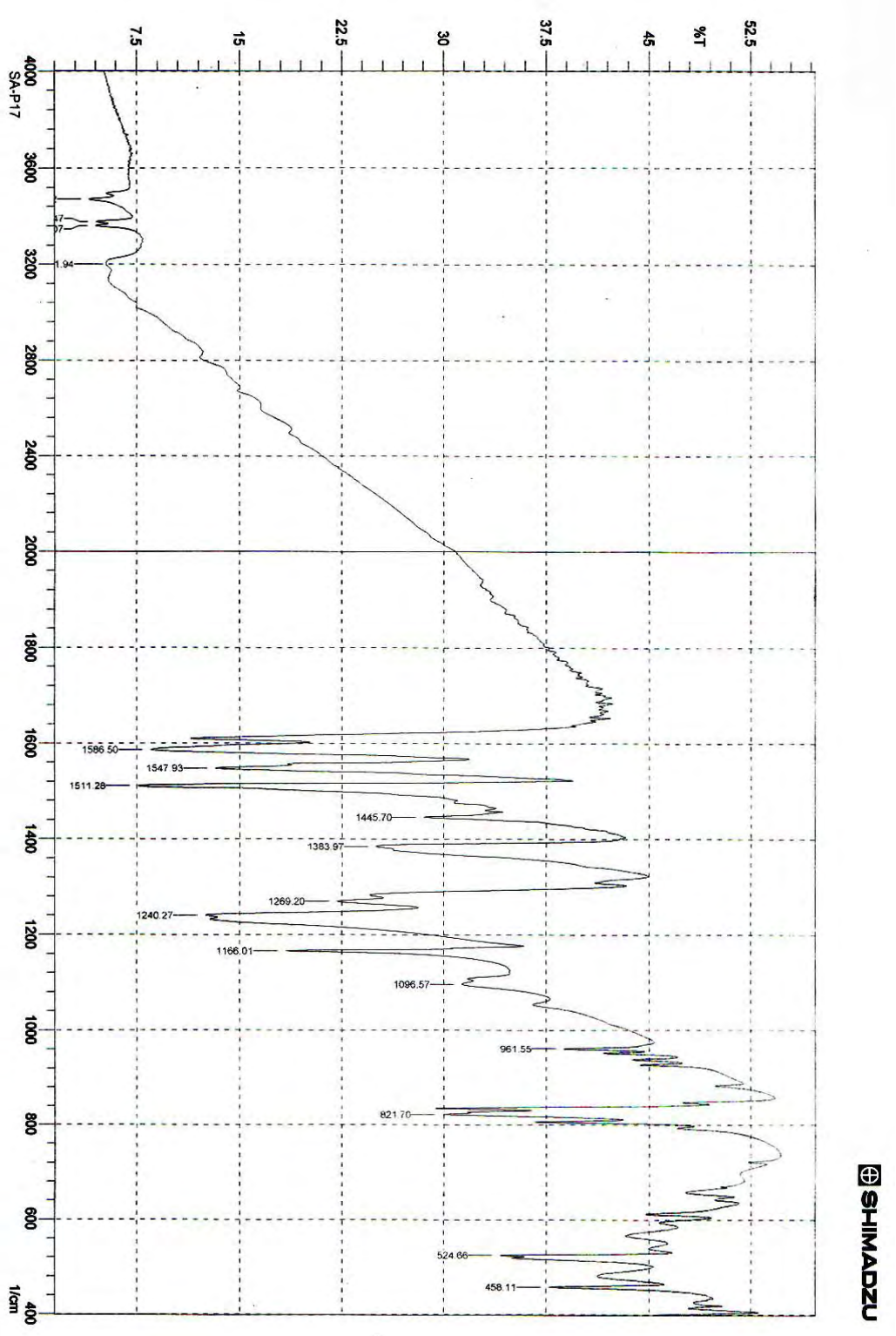


Figure 5: IR spectrum of compound 3(5′- *o*-hydroxyphenyl -1′, 3′, 4′-thiadiazolyl)-2(*p*-hydroxyphenyl)-thiazolidin-4-one

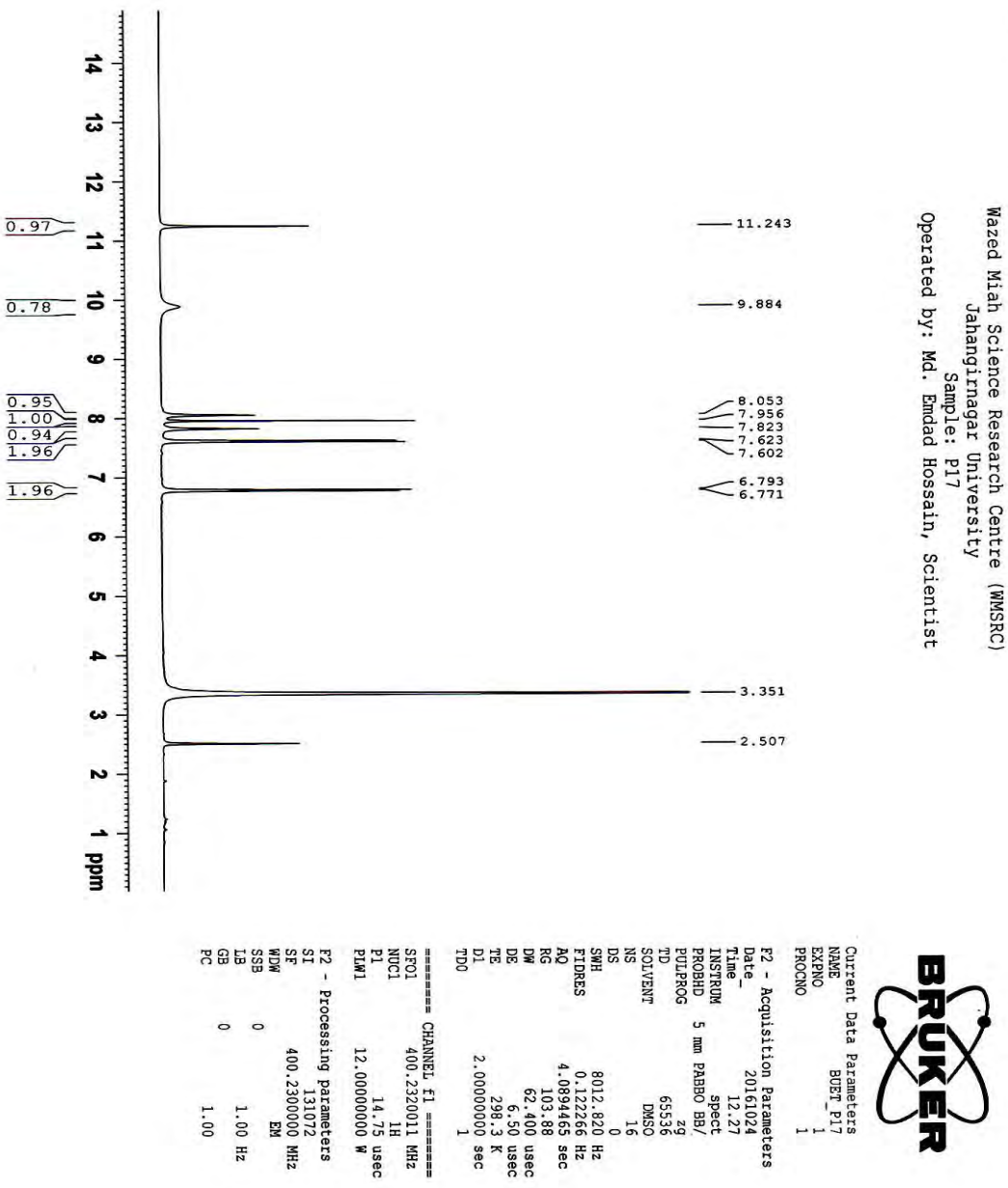


Figure 6: ^{1}H NMR of compound 3(5′- *o*-hydroxyphenyl -1′, 3′, 4′-thiadiazolyl)-2(*p*-hydroxyphenyl)-thiazolidin-4-one

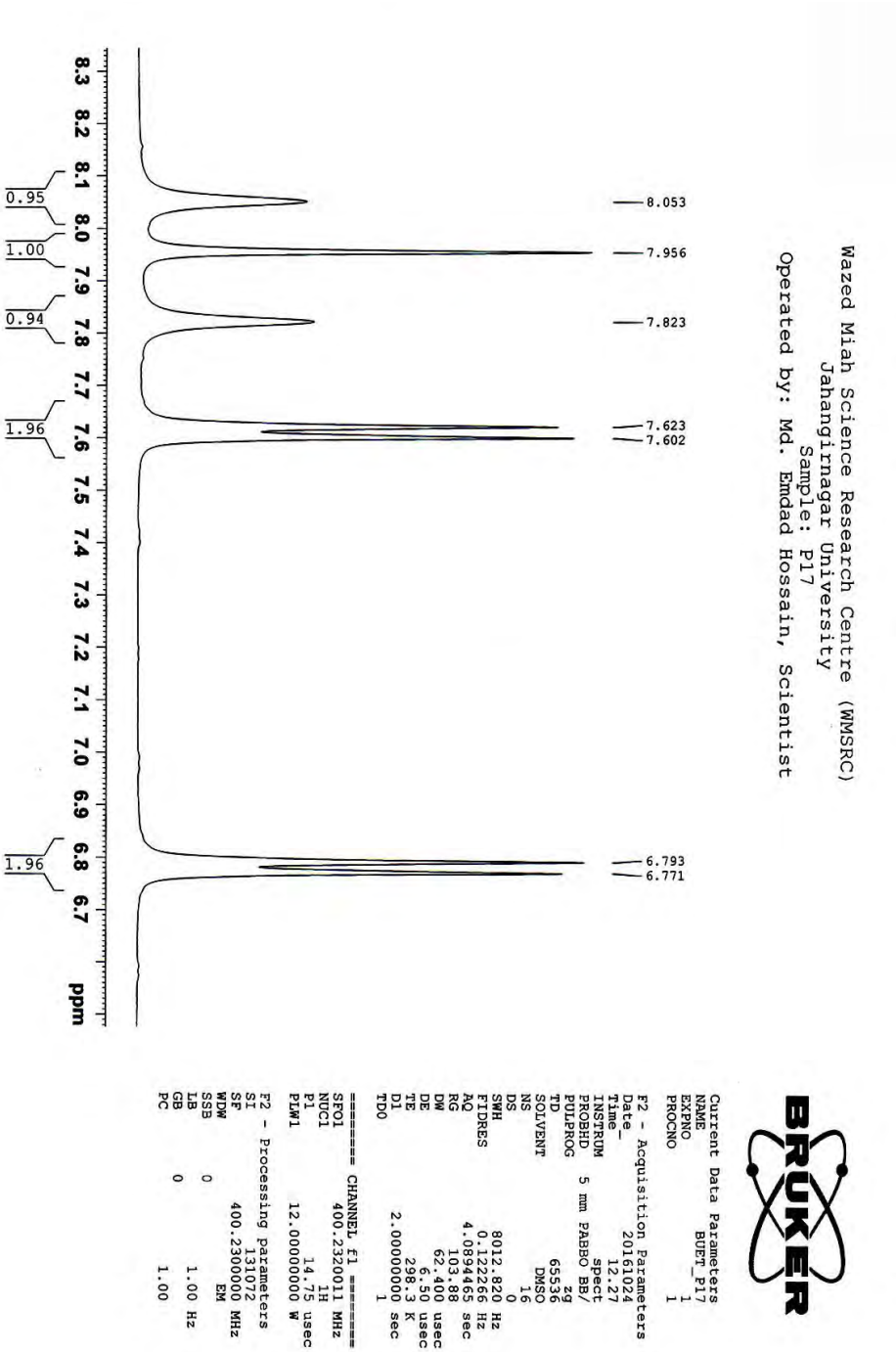


Figure 7: ^{1}H NMR (extention) of compound 3(5′- *o*-hydroxyphenyl -1′, 3′, 4′-thiadiazolyl)-2(*p*-hydroxyphenyl)-thiazolidin-4-one

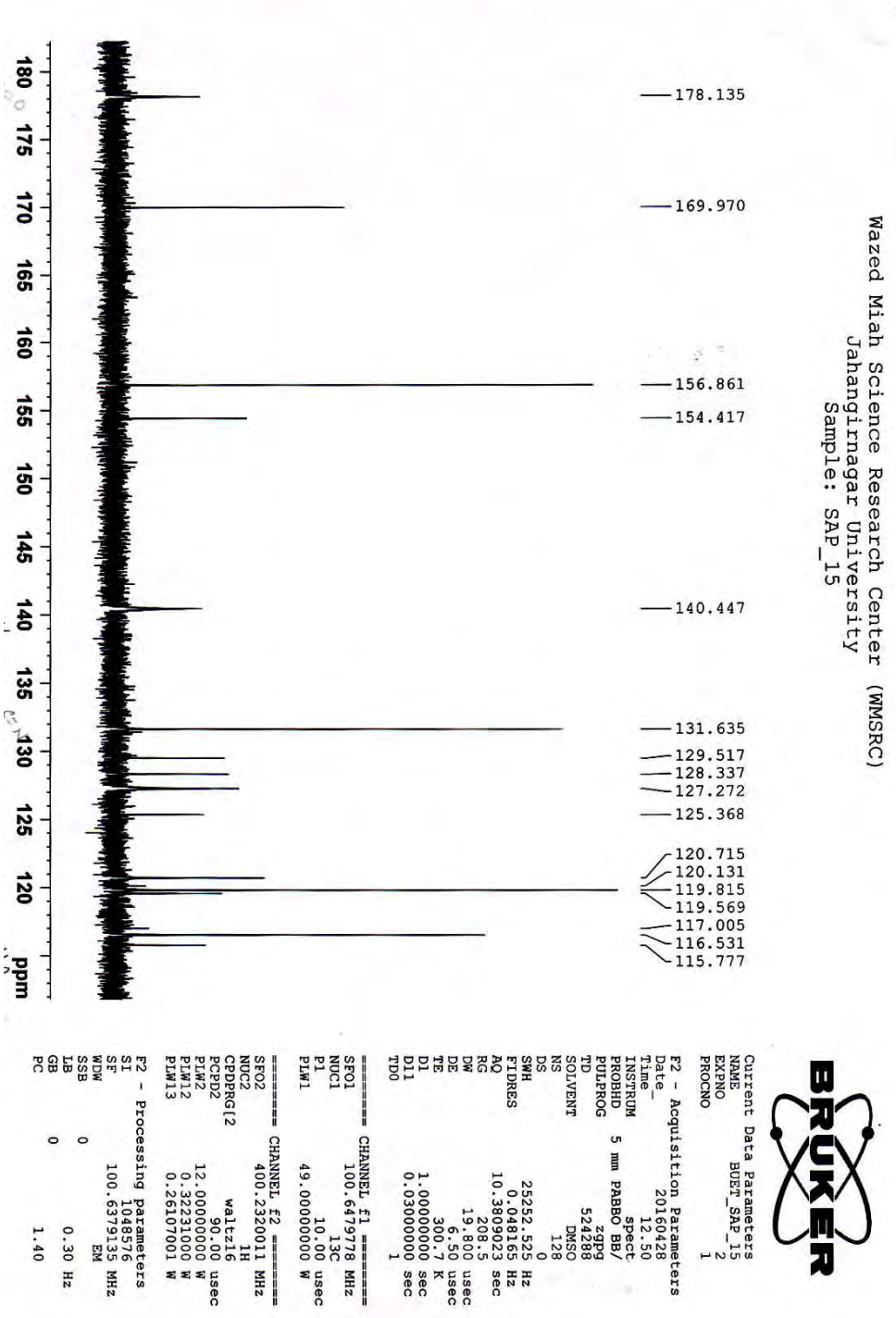
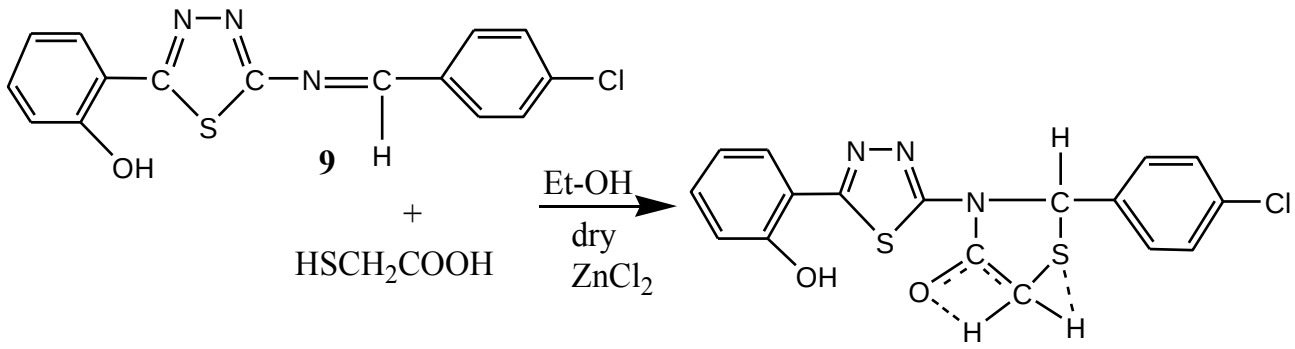


Figure 8: ^{13}C NMR of compound 3(5′- *o*-hydroxyphenyl -1′, 3′, 4′-thiadiazolyl)-2(*p*-hydroxyphenyl)-thiazolidin-4-one

3.3 Characterization of 3(5′- *o*-hydroxyphenyl -1′, 3′, 4′-thiadiazolyl)-2(*p*-chlorophenyl)-thiazolidin-4-one

The compound **19** was synthesized by refluxing equimolar mixture of 5(*o*-hydroxyphenyl)-2(*p*-chlorobenzylideneamino) -1, 3, 4-thiadiazole and mercapto acetic acid in ethanol in presence of catalytic amount of zinc chloride. The progress of the reaction was monitored by TLC. After work up, a white crystalline product with 78% yield was obtained and the melting point was recorded as $(206\text{-}209)^0$ C.

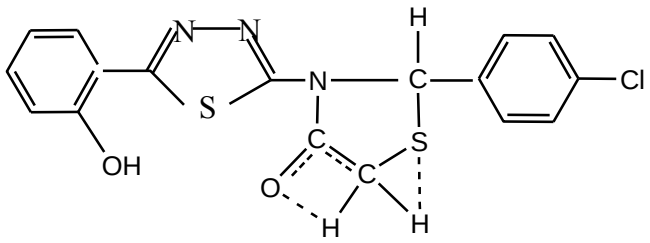


16 **19**

The IR spectrum (Fig. **9**) of the compound **19** showed a band at 3440 cm^{-1} was assigned for phenolic O-H group. The hydrogen bonded enolic O-H absorption was found at 3280 cm^{-1}. The peak at 3156 cm^{-1} was for typical aromatic C-H stretching. The aliphatic C-H stretching was identified at 2980 cm^{-1}. The hydrogen bonded C=O group was designated at comparatively longer wavelength 1650 cm^{-1}. The peak at 1600 cm^{-1} was distinctive for C=N. The characteristic peaks at 1520, 1491 and 1460 were detected for aromatic C=C. The C-S-C linkage was found at 815 cm^{-1}.

The ^{1}H NMR spectrum (Fig. **10**) of the compound **19** showed a broad singlet for two aromatic protons at 7.435-7.442. Another broad singlet for two aromatic protons were identified at 7.45-7.46. The broad signal at 7.802-7.806 was assigned for two aromatic protons and also another wide singlet of the same type was detective for two aromatic protons at 7.823. The signal at 8.023 was distinctive for one hydrogen bonded proton of C-CH_2-S. The single benzylic proton was designated in the merging signal at 8.023. The other single proton of C-CH_2-S was attributed at 8.174. The down fielded phenolic proton was indicative at 11.437.

All the above spectral evidences witnessed in favor of the structure **19** as



19

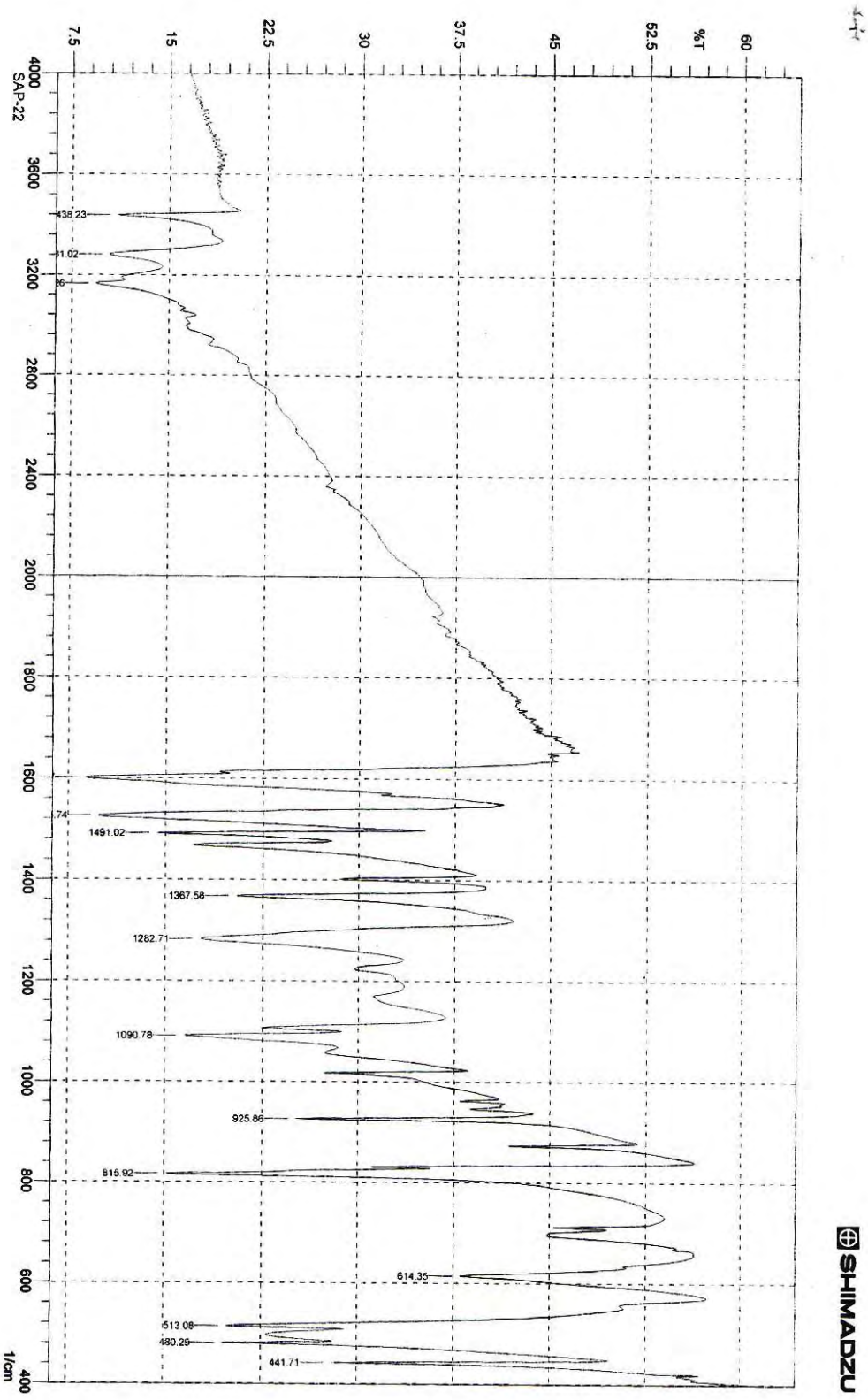


Figure 9: IR spectrum of compound 3(5′- *o*-hydroxyphenyl -1′, 3′, 4′-thiadiazolyl)-2(*p*-chlorophenyl)-thiazolidin-4-one

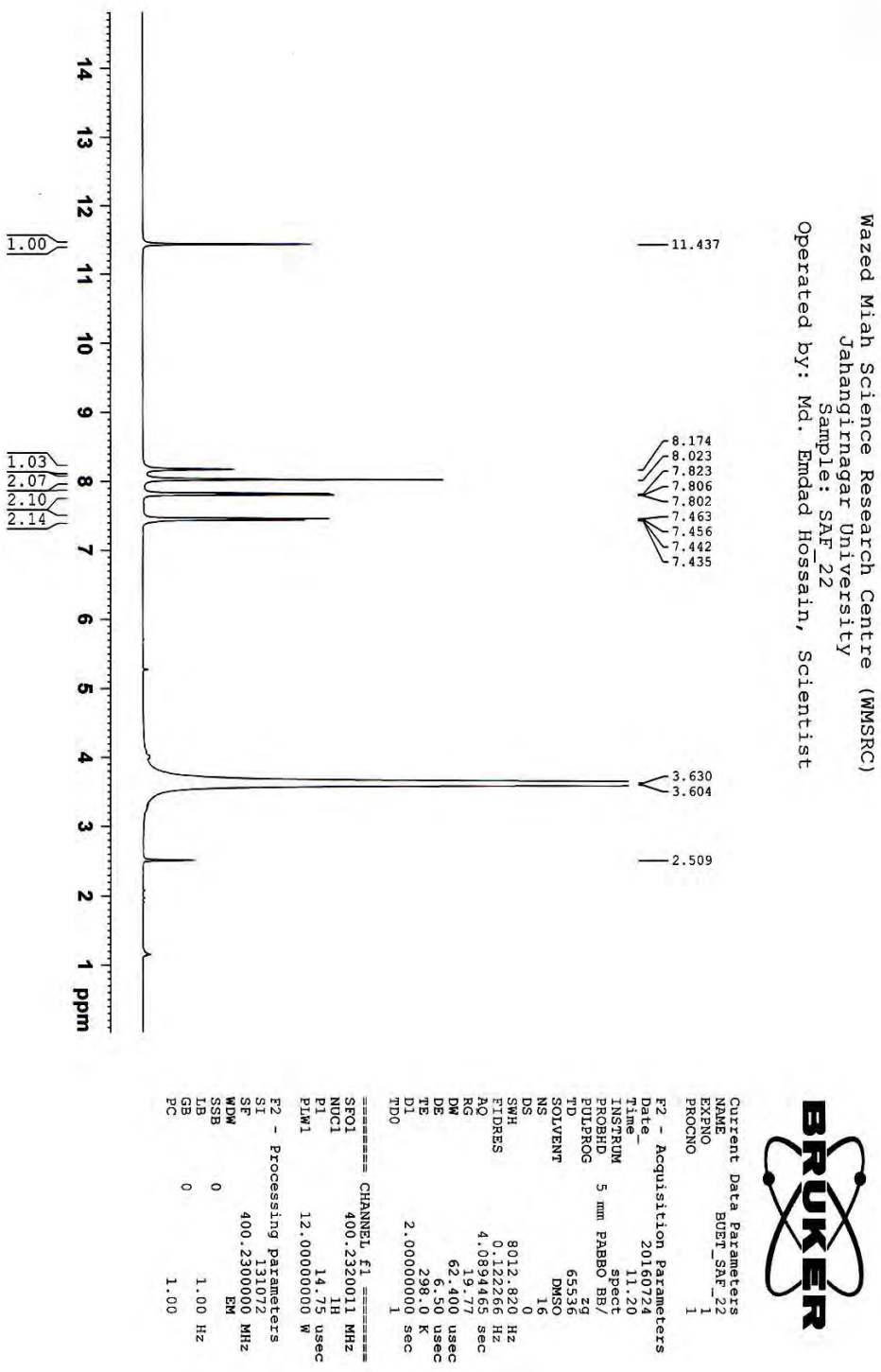
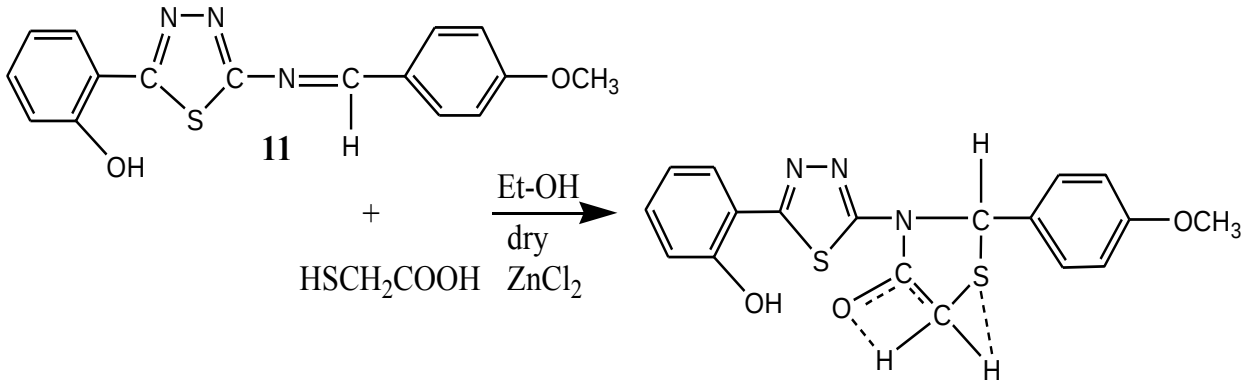


Figure 10: ^{1}H NMR of compound 3(5′- *o*-hydroxyphenyl -1′, 3′, 4′-thiadiazolyl)-2(*p*-chlorophenyl)-thiazolidin-4-one

3.4 Characterization of 3(5′- *o*-hydroxyphenyl -1′, 3′, 4′-thiadiazolyl)-2(*p*-methoxyphenyl)-thiazolidin-4-one

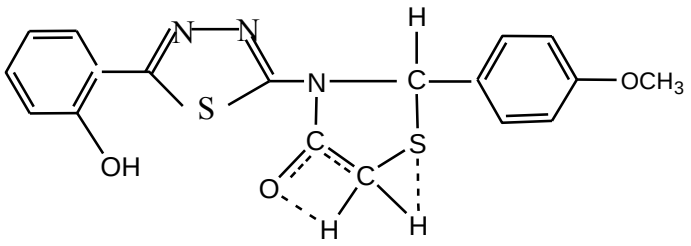
The compound **20** was synthesized by refluxing equimolar mixture of 5(*o*-hydroxyphenyl)-2(*p*-methoxybenzylideneamino) -1, 3, 4-thiadiazole and mercapto acetic acid in ethanol in presence of catalytic amount of zinc chloride. The progress of the reaction was followed by TLC. After work up, a white crystalline product with 76% yield was obtained and the melting point was recorded as (179-181) ^{0}C.



The IR spectrum (Fig. **11**) of the compound **20** showed a signal at 3400 cm^{-1} was assigned for phenolic O-H group. Another hydrogen bonded O-H peak was distinctive comparatively longer wavelength at 3290 cm^{-1}. The aromatic C-H stretching was found at 3153 cm^{-1}. The aliphatic C-H stretching was identified at 2990 cm^{-1}. The hydrogen bonded C=O group absorption was indicative comparatively longer wavelength at 1640 cm^{-1}. The C=N moiety was designated at 1600 cm^{-1}. The characteristic bands of aromatic C=C were identified at 1537, 1520 and 1440 cm^{-1}. The C-S-C linkage was vividly attributive at 835 cm^{-1}.

The ^{1}H NMR spectrum (Fig. **12**) of the compound **20** showed a sharp singlet of three protons of the OCH_3 group at 3.788. The four broad singlets, each of two aromatic protons were designated at 6.944, 6.966, 7.720 and 7.741. The wide deshielded singlet for one $–CH_2$ proton was distinctive at 7.903. The benzylic sharp singlet for one proton was assigned at 7.990. The other deshielded $–CH_2$ proton was identified at 8.099. The phenolic down fielded proton was attributed at 11.306.

All the above spectral evidences support the structure of the compound **20** as



20

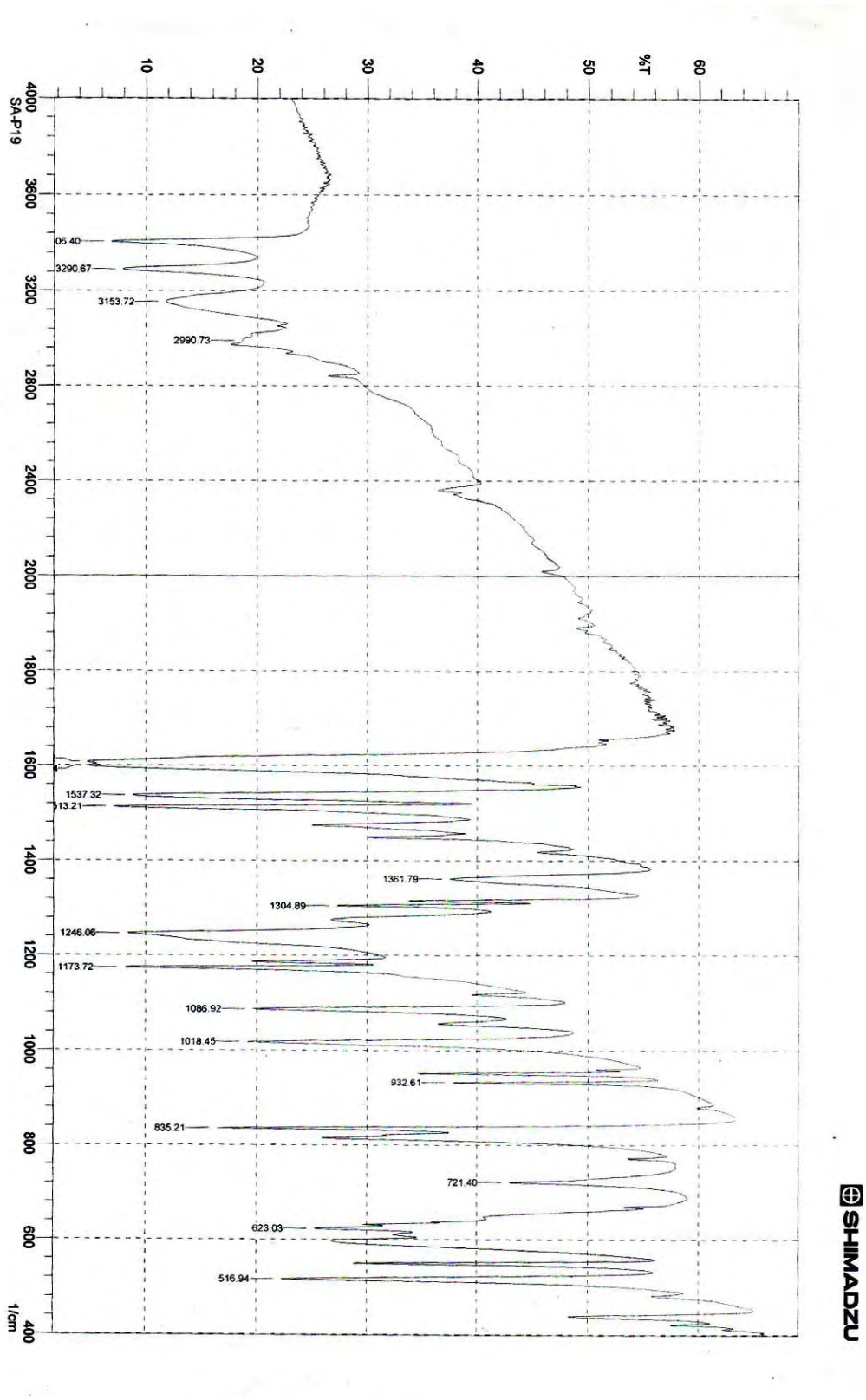


Figure 11: IR spectrum of compound 3(5′- *o*-hydroxyphenyl -1′, 3′, 4′-thiadiazolyl)-2(*p*-methoxyphenyl)-thiazolidin-4-one

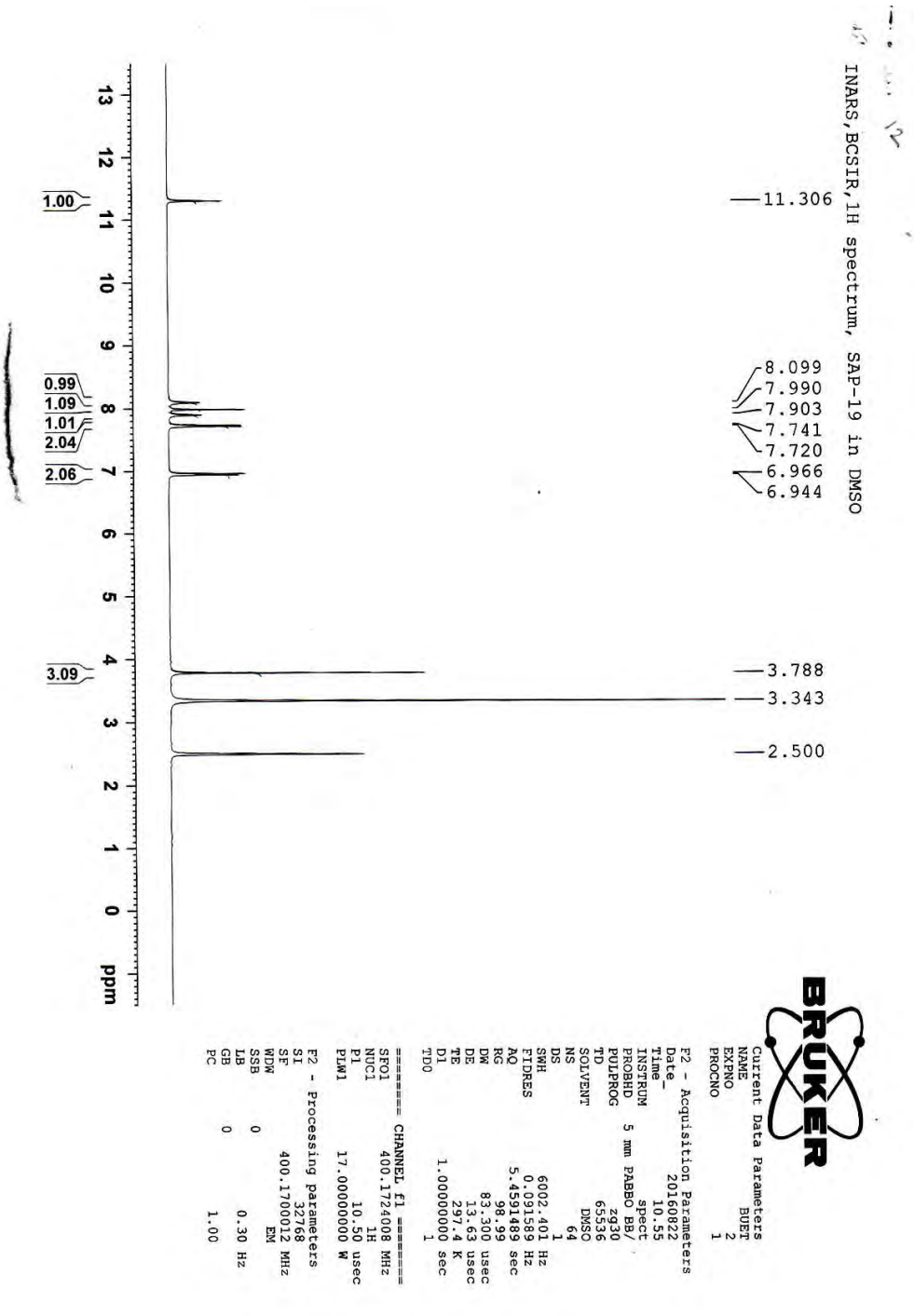
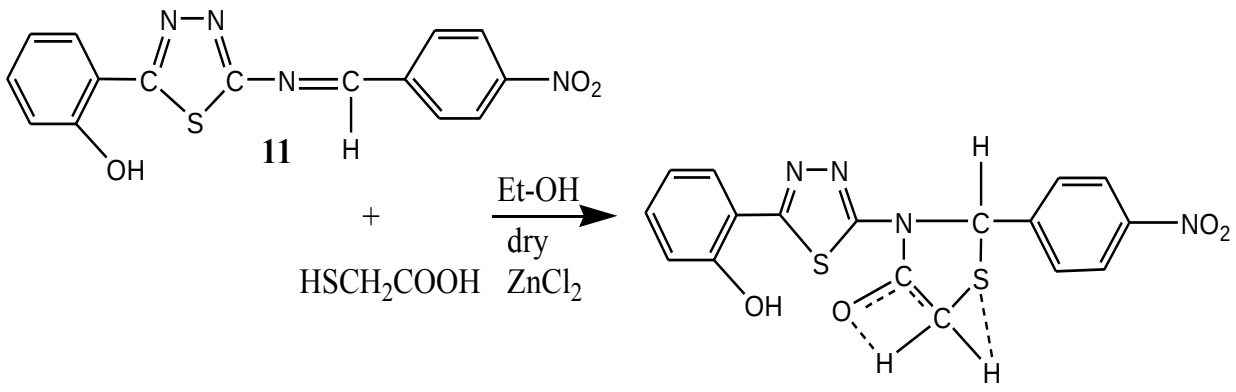


Figure 12: ^{1}H NMR of compound 3(5′- *o*-hydroxyphenyl -1′, 3′, 4′-thiadiazolyl)-2(*p*-methoxyphenyl)-thiazolidin-4-one

3.5 Characterization of 3(5′- *o*-hydroxyphenyl -1′, 3′, 4′-thiadiazolyl)-2(*p*-nitrophenyl)-thiazolidin-4-one

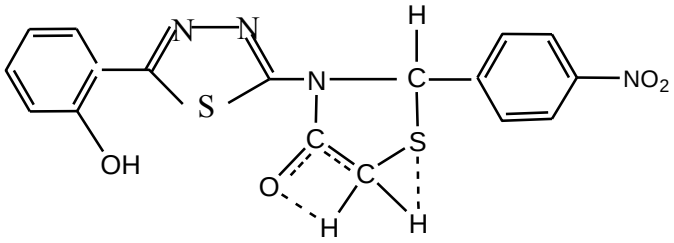
The compound **21** was synthesized by refluxing equimolar mixture of 5(*o*-hydroxyphenyl)-2(*p*-nitrobenzylideneamino) -1, 3, 4-thiadiazole and mercapto acetic acid in ethanol in presence of catalytic amount of zinc chloride. The progress of the reaction was followed by TLC. After work up, the yellow crystalline product with 64% yield was obtained and the melting point was recorded as (243-245) ^{0}C.



The IR spectrum (Fig. **13**) of the compound **21** showed a signal at 3480 cm^{-1} was assigned for phenolic O-H group. The peak at 3367 cm^{-1} was indicative for hydrogen bonded enolic O-H. The aromatic C-H stretching was designated at 3148 cm^{-1}. The aliphatic C-H stretching was identified at 2996 cm^{-1}. The weak peak at 1650 cm^{-1} was distinctive for hydrogen bonded C=O group. The C =N absorption band was attributed at 1580 cm^{-1}. The characteristic aromatic C=C bond were identified at 1577, 1516 and 1453 cm^{-1}. The peak at 1340 cm^{-1} was ascribed for N=O. The typical C-S-C linkage was found at 820 cm^{-1}.

The ^{1}H NMR spectrum (Fig. **14**) showed four signals as broad singlet of two aromatic protons in each signal at 8.090, 8.112, 8.131 and 8.219. The singlet of one benzylic proton was designated at 8.241. The wide singlet of one deshielded –CH_2 proton was distinctive at 8.262. The other deshielded signal for one proton of –CH_2 was identified at 8.404. The down field deshielded proton of phenol was designated at 11.171.

All the above spectral evidences support in favor of the structure of the compound **21** as



21

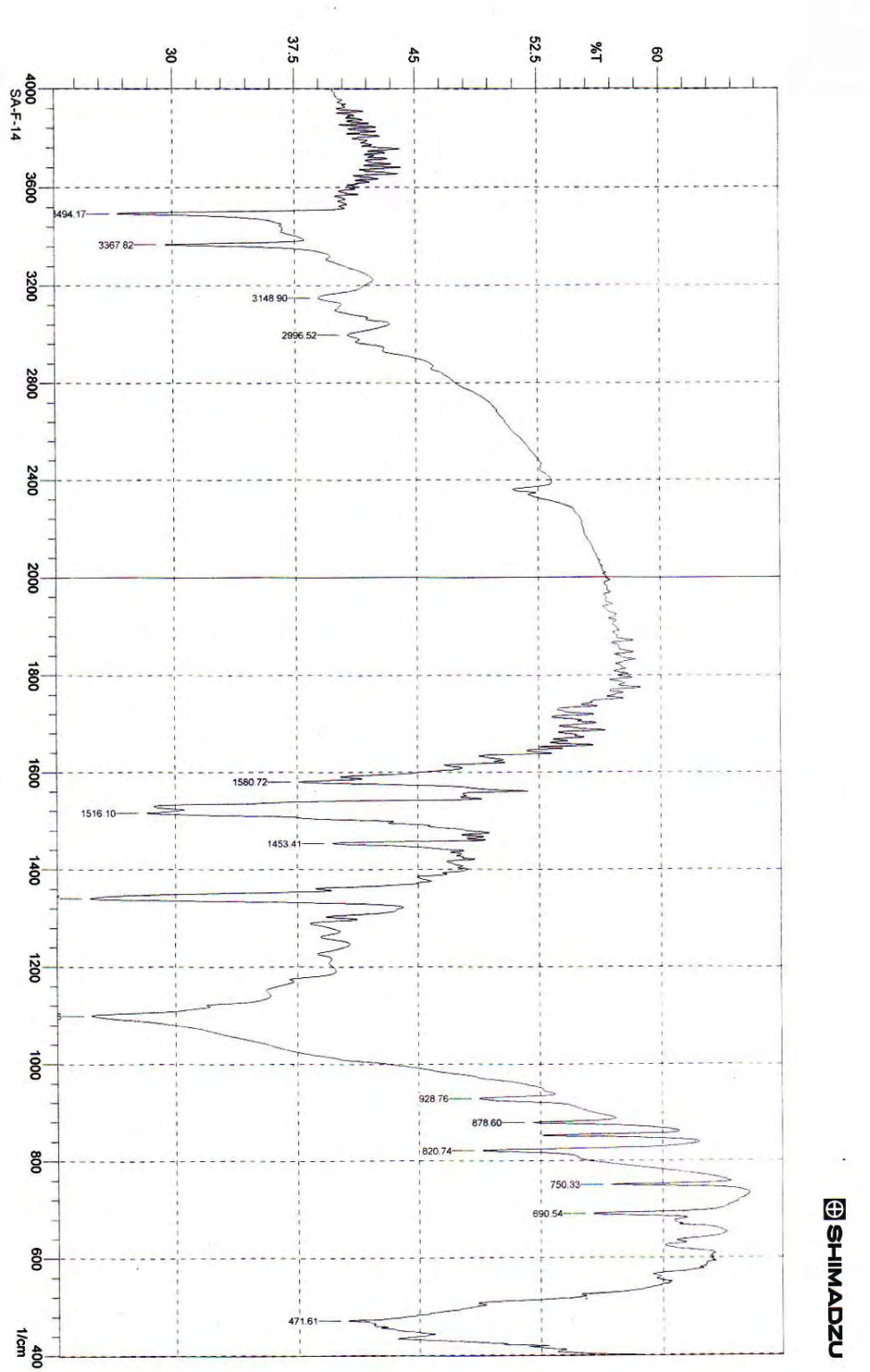


Figure 13: IR spectrum of compound 3(5′- *o*-hydroxyphenyl -1′, 3′, 4′-thiadiazolyl)-2(*p*-nitrophenyl)-thiazolidin-4-one

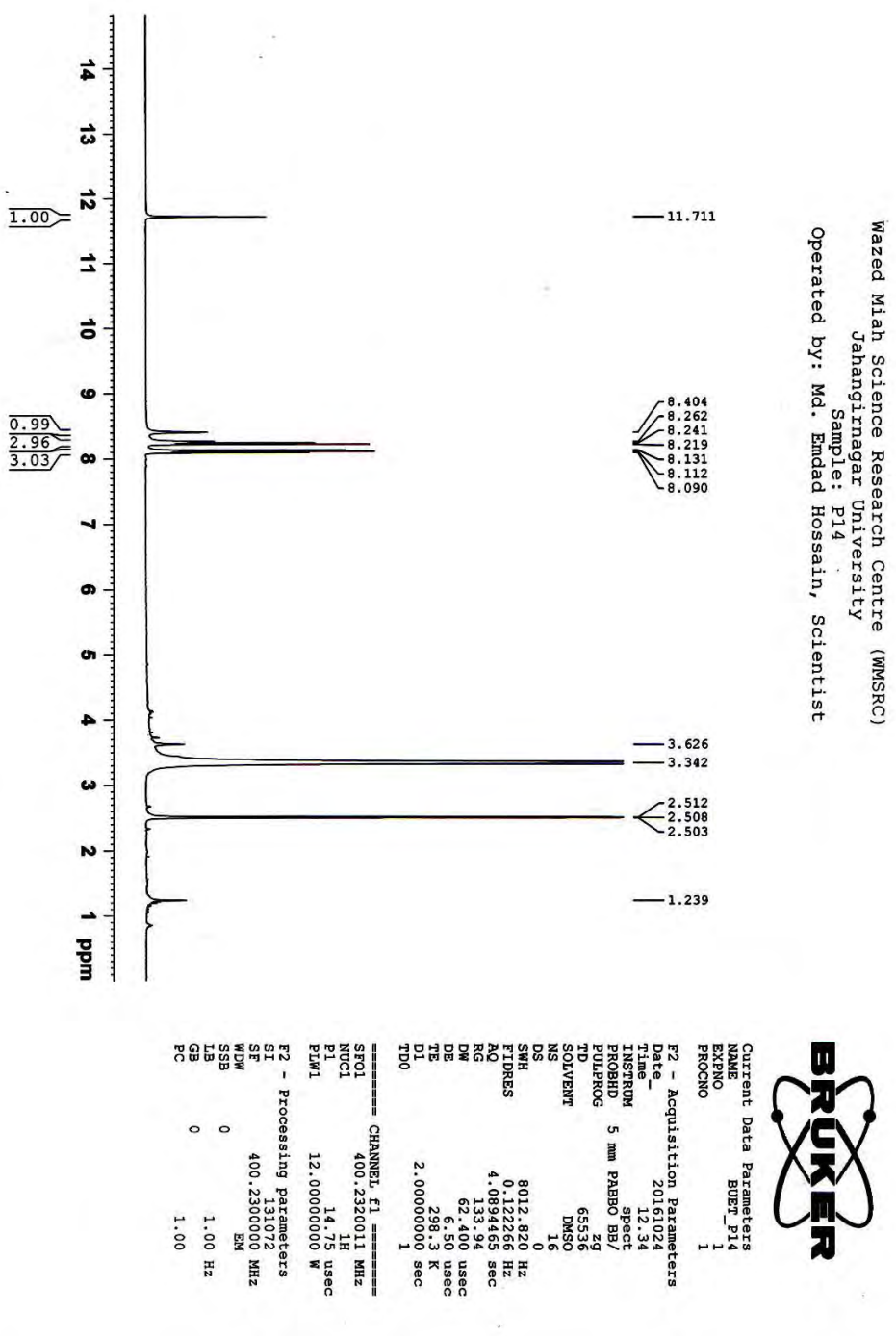
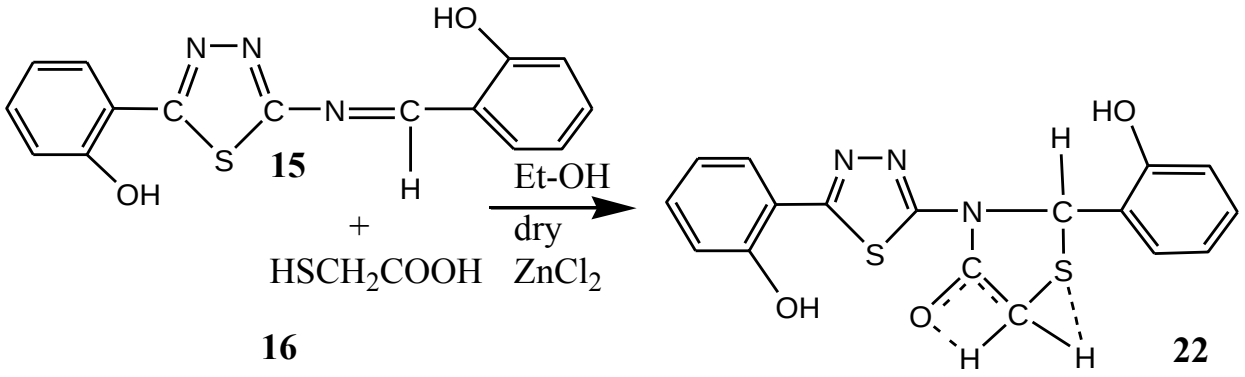


Figure 14: ^{1}H NMR of compound 3(5′- *o*-hydroxyphenyl -1′, 3′, 4′-thiadiazolyl)-2(*p*-nitrophenyl)-thiazolidin-4-one

3.6 Characterization of 3(5′- *o*-hydroxyphenyl -1′, 3′, 4′-thiadiazolyl)-2(*o*-hydroxyphenyl)-thiazolidin-4-one

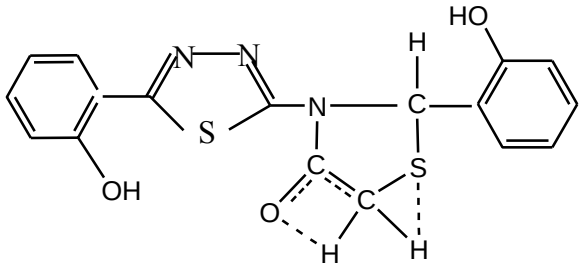
The compound **22** was synthesized by refluxing equimolar amount of 5(*o*-hydroxyphenyl)-2(*o*-hydroxybenzylideneamino) -1, 3, 4-thiadiazole and mercapto acetic acid in ethanol in presence of catalytic amount of zinc chloride. The progress of the reaction was followed by TLC. After work up, a reddish yellow crystalline solid with 69% yield was obtained and the melting point was recorded as (216-219) ^{0}C.



The IR spectrum (Fig. **15**) of the compound **22** showed a band at 3445 cm^{-1} was assigned for phenolic O-H group. The other O-H peak was distinctive at 3320 cm^{-1}. The characteristic aromatic C-H stretching was identified at 3147 cm^{-1}. The peak at 2936 cm^{-1} was designated for aliphatic C-H stretching. The deshielded keto-enol tautomerised C=O group was indicative comparatively longer wavelength 1640 cm^{-1}. The C =N moiety was attributed at 1600 cm^{-1}. The characteristic peaks at 1500, 1490 and 1446 cm^{-1} were ascribed for aromatic C=C. The C-S-C linkage was found at 830 cm^{-1}.

The ^{1}H NMR spectrum (Fig. **16**) of the compound showed a broad multiplet at 6.802-6.875 was assigned for five aromatic protons. The rest four aromatic protons were designated as multiplet at 7.196-7.238. A wide peak of single CH_2 proton was distinctive 7.882-7.899. Another hydrogen bonding deshielded –CH_2 proton was suggestive at 8.053. The single benzylic proton was identified at 8.372. The two phenolic O-H protons were distinctive at 9.960 and 11.358 respectively.

All the above spectral evidences expressed harmony with the structure of the compound **22** as



22

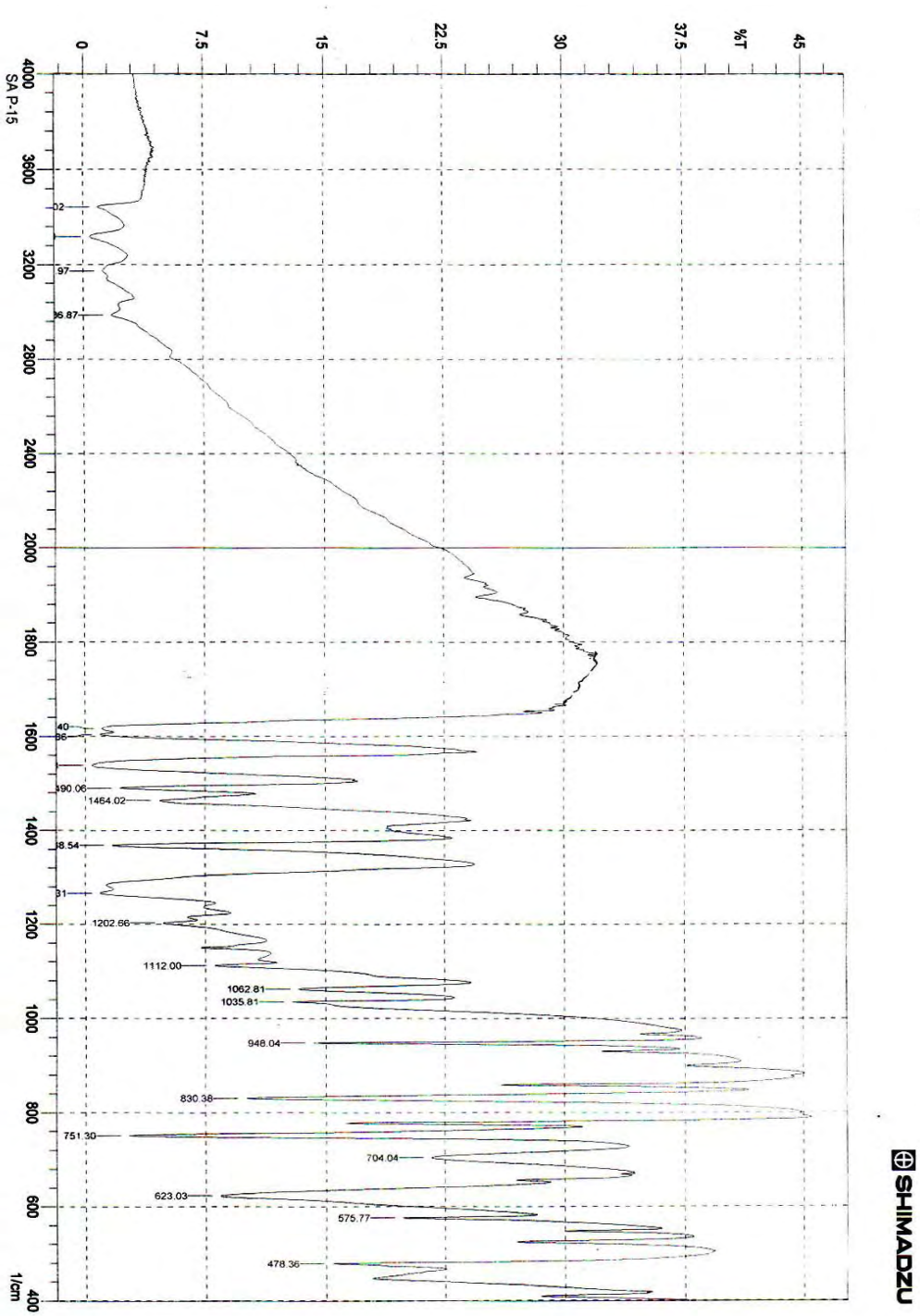


Figure 15: IR spectrum of compound 3(5′- *o*-hydroxyphenyl - 1′, 3′, 4′-thiadiazolyl)-2(*o*-hydroxyphenyl)-thiazolidin-4-one

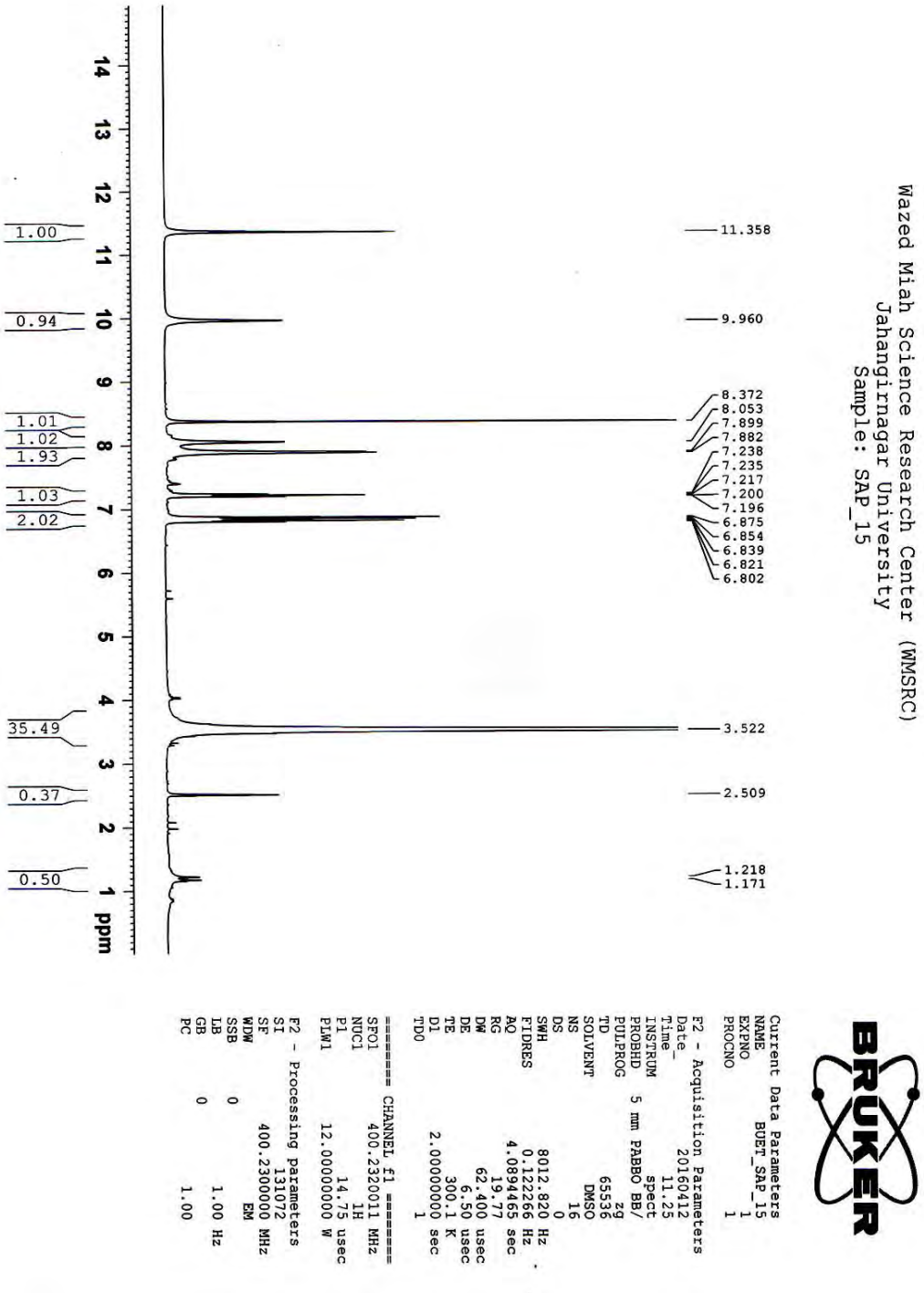


Figure 16: ^{1}H NMR of compound 3(5′- *o*-hydroxyphenyl - 1′, 3′, 4′-thiadiazolyl)-2(*o*-hydroxyphenyl)-thiazolidin-4-one

Chapter 4
Biological test

4.1 Antibacterial and Antifungal test

Thiazolidinone derivatives **10** and **11** were tested for the antibacterial and antifungal activity against *E.coli* and *A.niger* as shown in the table below.

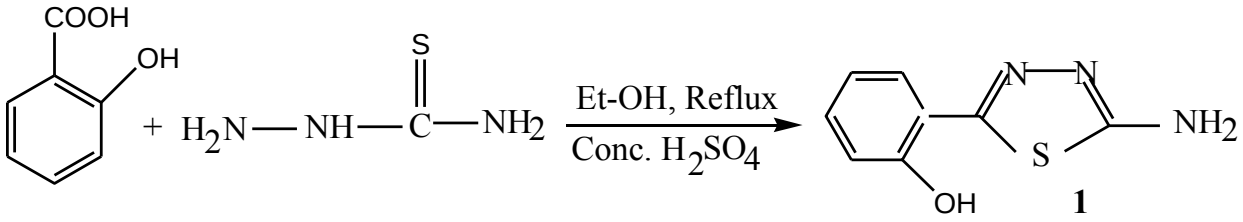
SL. No.	Tested organisms against antimicrobial activity	Diameter of inhibition zone(mm)	
		P-10(40mg/ml)	P-11(40mg/ml)
1	*Escherichia coli*	9	7
2	*Aspergillus niger*	8	5

This table distinctively showed moderate activity against *E.coli* and *A.niger*.

Summary

1. Synthesis of thiadiazole

A mixture of thiosemicarbazide, salicylic acid and concentrated sulfuric acid in ethanol was stirred under reflux condition for one hour and 50 minutes. The reaction mixture was then poured into crushed ice and the crude product was separated by filtration. The crude was purified by recrystallization from ethanol.

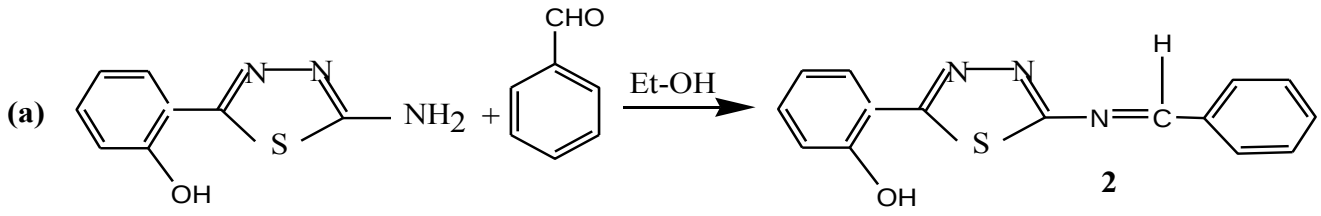


1

Yield: 82%
m.p:(145-150) ^oC

2. Synthesis of Hydrazones

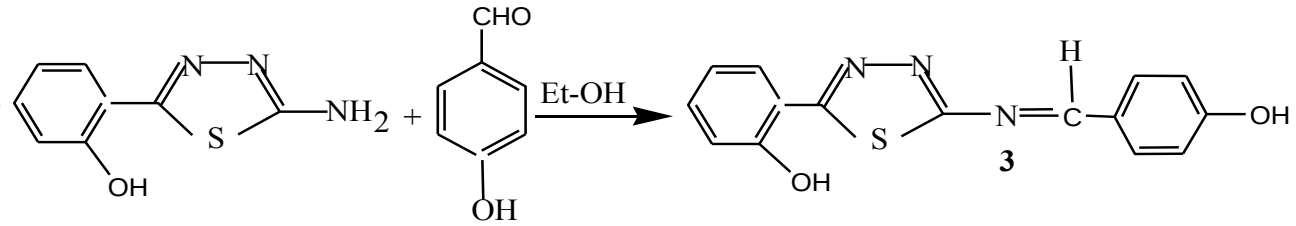
A solution of thiadiazole and different substituted benzaldehydes in ethanol were stirred under reflux condition for 1.5-2.5 hours. The progresses of the reactions were monitored by TLC. The reaction mixtures were then poured into ice water. Different crude hydrazones were separated by filtration and used for the synthesis of thiazolidinone derivative.



2

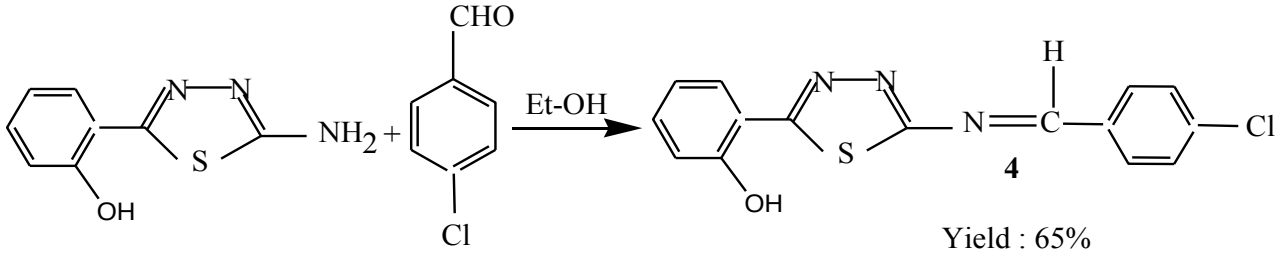
Yield: 63%
m.p:(162-165) ^oC

(b)



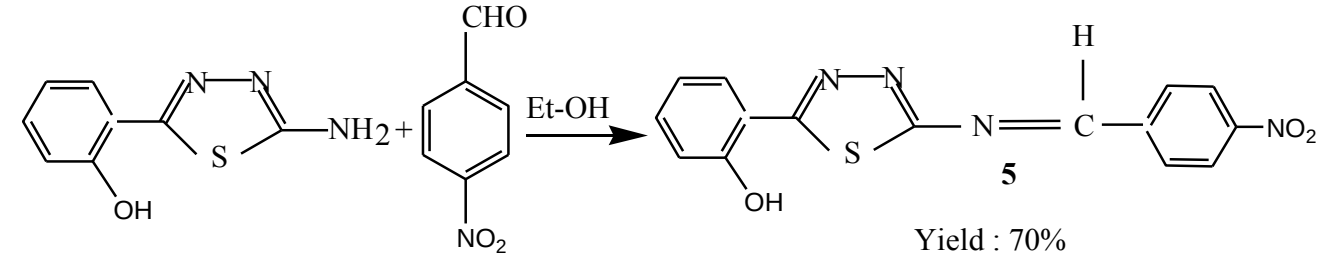
Yield :71%
m.p:(218-221) ^{o}C

(c)



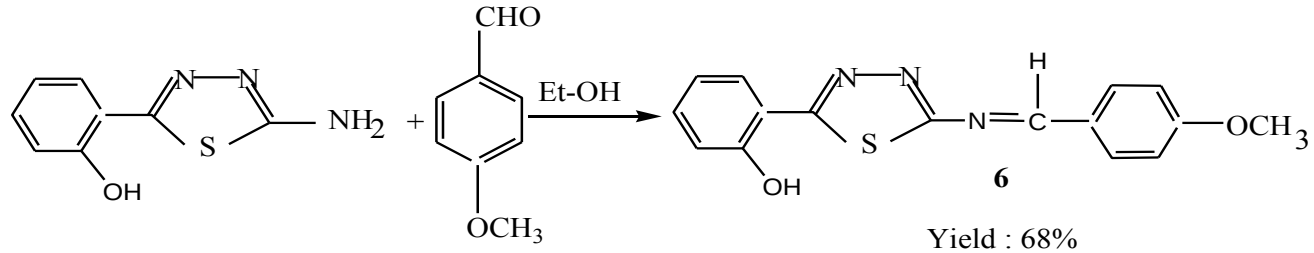
Yield : 65%
m.p:(219-220) ^{o}C

(d)



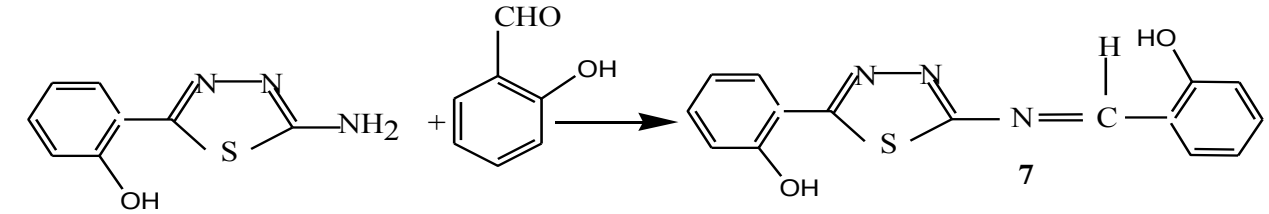
Yield : 70%
m.p :(237-239) ^{o}C

(e)



Yield : 68%
m.p :(172-178) ^{o}C

(f)

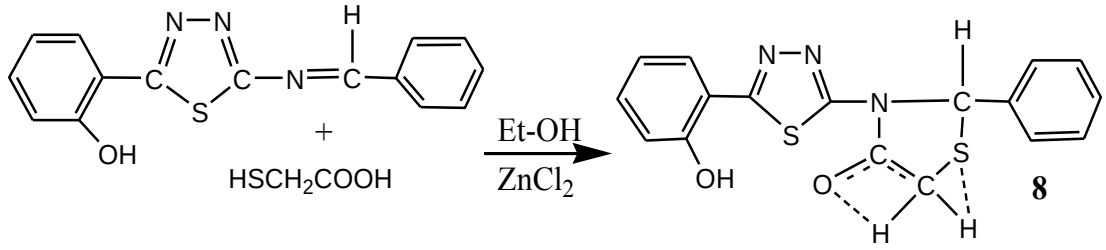


Yield : 73%
m.p :(195-203) ^{o}C

3. Synthesis of Thiazolidinone derivatives

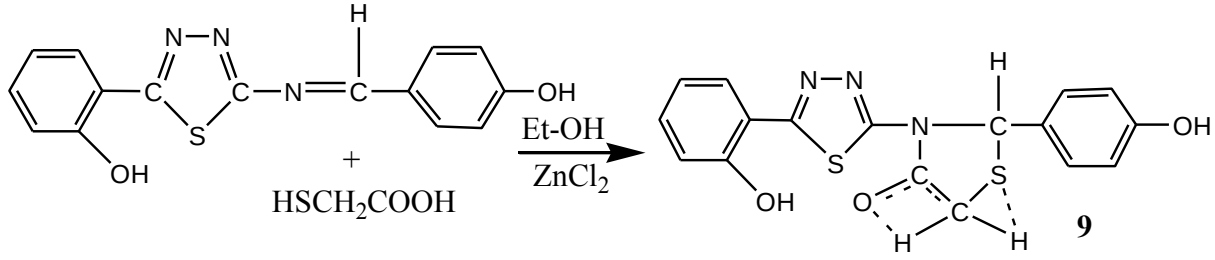
A solution of different hydrazones and mercapto acetic acid in ethanol were refluxed 10-12 hours in presence of catalytic amount of zinc chloride. The progresses of the reactions were monitored by TLC. After completion of the reactions, the mixtures were poured into ice water and the different coulered solid crude materials were separated by filtration. The crude products were then purified by recrystallization from ethanol and characterized by spectral evidences such as IR, ^{1}H NMR and ^{13}C NMR.

(a)



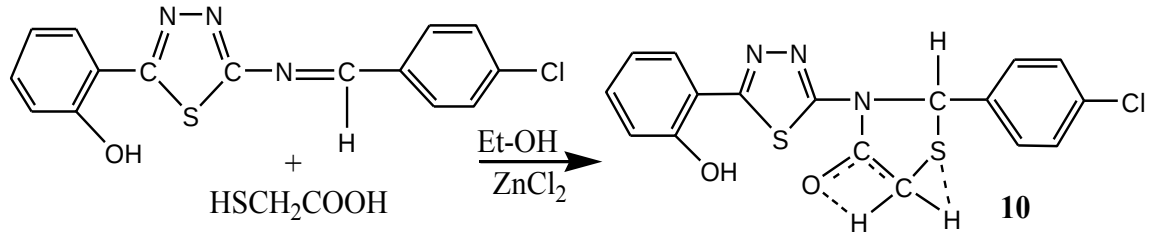
Yield : 67%
m.p: (178-185) ^{o}C

(b)

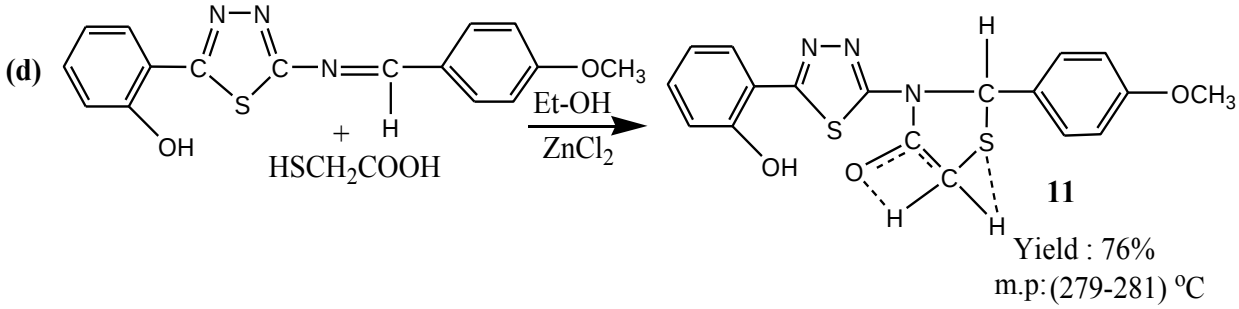


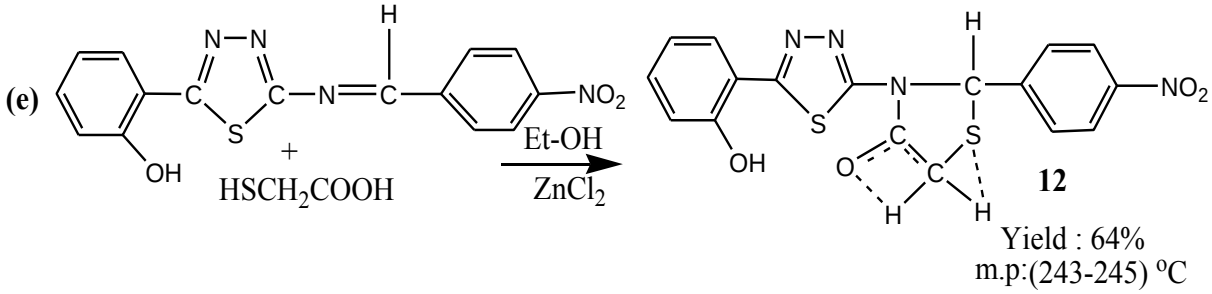
Yield : 62%
m.p :(239-241) ^{o}C

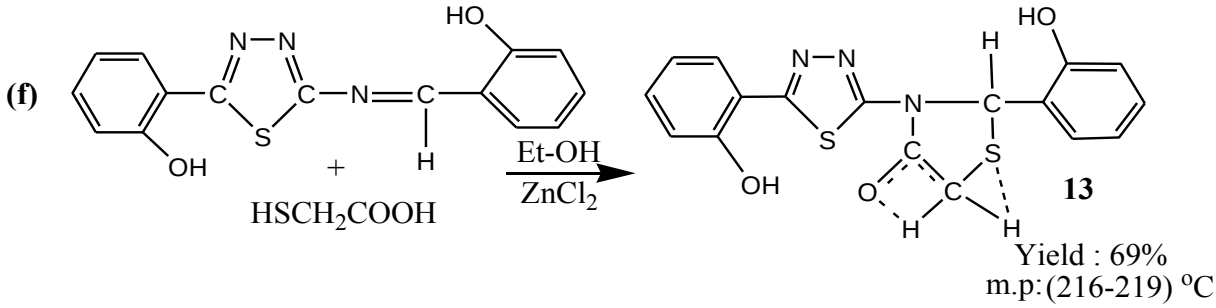
(c)



Yield : 78%
m.p:(206-209) ^{o}C







4. Biological activity

The antibacterial and antifungal properties of thiazolidinone derivatives **10** and **11** showed moderate activity against *Escherichia coli* and *Aspergillus niger*.

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